6-Minute walk distance in healthy North Africans older than 40 years: Influence of parity

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Summary
The need for a 6-min walk distance (6-MWD) reference equation for healthy North African adults older than 40 years was assessed in a prospective cross-sectional study.

Anthropometric data and 6-MWD were measured in 229 healthy Tunisian adults (125 women) over 40 years old. Two subgroups of 38 women were identified according to the parity (low / high). The published reference equations did not reliably predict measured 6-MWD. The 6-MWD was significantly correlated with gender, age, weight and height (p < 0.001). The combination of these parameters explained 77% of the 6-MWD variability in the equation: 6-MWD (m) = −160.27 + 5.14gender (0: men; 1: women) + 2.23age (yr) + 2.72weight (kg) + 720.50height (cm). Parity accelerated the 6-MWD decline (r = −0.39, p < 0.05) and women distinguished only by parity (low / high) showed different 6-MWD (589 ± 60 m vs. 555 ± 57 m, p < 0.05). In an additional group of

Abbreviations: ATS, American thoracic society; BMI, body mass index; DP, diastolic pressure; ECG, electrocardiogram; FEV1, forced expiratory volume in 1 s; FEF, forced expiratory flow between 25% and 75% of the forced vital capacity; FVC, forced vital capacity; Hr, heart rate; LLN, lower limit of normal; p, probability; PEF, peak expiratory flow; r, correlation coefficient; r², determination coefficient; sat, oxyhemoglobin saturation; SEL, socioeconomic level; SL, schooling level; 6-MWT, six-min walk test; 6-MWD, six-min walk distance; SP, systolic pressure; VAS, visual analogue scale; 1, before the 6-MWT; 2, after the 6-MWT.

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Introduction

The 6-min walk test (6-MWT) assesses exercise tolerance by measuring the distance that a subject can walk quickly on a flat, hard surface in 6 min (6-MWD). The interpretation of this test, which is more reflective of daily living activities than other walk tests, relies on the comparison of measured 6-MWD with the predicted distance.

Anthropometric data [gender, age, height, weight, body mass index (BMI)] explain from 34% to 66% of 6-MWD variability, but other factors are influential. Nevertheless, the relationships between 6-MWD and resting spirometric data, cardiovascular data measured before/after the 6-MWT, activity scores, and socioeconomic or schooling levels (SEL, SL) are not well established. Also, the relationship between 6-MWD and parity, a particular factor in developing nations [4.3 in Tunisia; 1.6 in Europe and North America] has not been analyzed. High parity has deleterious effects on health, including high risks of heart disease, obesity, renal cancer, and accelerated decline in pulmonary function. Repeated gestations may have consequences on submaximal aerobic capacity as evaluated by the 6-MWD.

No local or North African 6-MWD reference equations exist for Tunisian adults, and interpretation of results is thus based on the published equations. This is a questionable practice, however, since their reliability has never been verified in this population, even though several specificities have been noted regarding: ethnic background, anthropometric data, sedentary lifestyle, SEL, SL, parity, etc. In addition, among the six studies that provided 6-MWD reference equations, only one prospectively verified the reliability in their population. A method to interpret measured 6-MWD was proposed in only three studies: use of the lower limit of normal (LLN) or a fixed percentage, below which the 6-MWD is considered as abnormal.

In North African adults, the need for specific local reference equations has been shown, at least for spirometric data. The applicability and reliability of the published 6-MWD reference equations should also be assessed, because the use of non-North African equations may lead to erroneous clinical interpretation of 6-MWT. Further, the American Thoracic Society (ATS) encourages investigators to publish reference equations for healthy persons using the 6-MWT guidelines.

The aims of the present study were the following: (1) to determine the factors influencing 6-MWD in healthy North Africans older than 40 years, with particular attention to parity, (2) to test the applicability and reliability of the previously published reference equations in this population, and, if needed, (3) to establish a reference equation for 6-MWD and prospectively assess its reliability.

Methods

We performed this prospective study over a 6-month period in the Physiology and Functional Exploration Department of Farhat Hached Hospital in Sousse, Tunisia.

Study design

Subjects were recruited among hospital workers and the parents of medical school students. Informational letters clarifying the aims of the study were put up in the hospital departments and the School of Medicine. Data from each volunteer adult included: gender, age, height, weight, parity, SL, SEL, smoking history, medication use, medical history, physical examination, physical activity questionnaire, spirometry and electrocardiogram (ECG). The 6-MWT procedure was then performed. All subjects received a copy of their exploration results and when an unsuspected dysfunction was discovered, they were sent to a specialist. Approval for the study was obtained from the hospital ethics committee, and written informed consent was obtained from all study participants.

Sample size

As for spirometry, a relatively large number of subjects (i.e. ≥100) is necessary to ensure no significant difference between the published reference equations and the values from the local community. Therefore, to determine influencing factors and a reference equation, we included an initial group of 125 women and 104 men.

To determine the parity effect, a predictive equation of the sample size was calculated: \[ n = \left( \frac{Z_{\alpha/2} \times p \times q}{d^2} \right)^2 \], where \( n \) was the number of required women in the 45–59 age range, \( Z \) was the 95% confidence level, \( q = 1 - p \) was equal to \( 1 - p \), \( d \) was the precision (≒7%), and \( p \) was the estimation of the 6-MWD decline induced by high parity. As, to our knowledge, no study has documented this effect, we chose as a reference the relationship between parity and forced expiratory volume (FEV₁) \( r^2 = 0.11 \). The sample size was thus 76 women.

To verify the reliability of our 6-MWD reference equation, we prospectively measured 6-MWD in a second group of 30 additional healthy adults (15 women) who met the study inclusion criteria and had not participated in the first part.

Subjects

Healthy voluntary adults ≥40 years were included. Detailed non-inclusion criteria appear in the Supplementary data.

Briefly, they included the usual relative 6-MWT contraindications, current smoking, cardiopulmonary, metabolic and...
orthopedic disease, marked and extreme obesity or underweight, chronic medication use, and inability to perform the 6-MWT exactly.

Medical and physical activity questionnaires

A medical questionnaire recommended for epidemiological research was used to assess several subject characteristics. Two SL were defined: low (illiterate, primary education) and high (secondary and university education). Two SEL were defined according to occupational status: low (e.g. unskilled worker, jobless) and high (e.g. skilled worker, farmer, manager). A translated version of the Voorrips et al. physical activity questionnaire was filled out by each subject, and household, sporting, and leisure activities were evaluated to yield a total physical activity score (low: <9.4, moderate: 9.4–16.5, and high: ≥16.5).21

Physical examination and parity

Age (yr) was verified by the identity card. Height (±0.01 m) was measured with a height gauge with shoes removed, heels joined, and back straight. Weight (±1 kg) was measured and BMI was calculated (=weight/height²). The following definitions were adopted: underweight (BMI < 18.5 kg/m²), normal weight (18.5 kg/m² ≤ BMI ≤ 24.9 kg/m²), overweight (25 kg/m² ≤ BMI ≤ 29.9 kg/m²), moderate obesity (30 kg/m² < BMI ≤ 34.9 kg/m²), marked obesity (35 kg/m² < BMI ≤ 39.9 kg/m²) and extreme obesity (BMI ≥ 40 kg/m²).

Parity referred to the number of offspring. In the women with ages between 45 and 59 years, two parity subgroups (n = 38 each) were identified: low and high (parity ≤ 5 and ≥ 6, respectively).11

Spirometry and ECG

Spirometric measurements (PAL, MINATO, Japan) were performed according to international recommendations.23 The results [FEV₁, forced vital capacity (FVC), FEV₁/FVC, peak expiratory flow (PEF), and forced mid-expiratory flow between 25% and 75% of the FVC (FEF)] were compared with local age- and gender-matched reference values.12,16

Next, a 12-lead resting ECG was performed.

6-MWT procedure

The 6-MWT was conducted according to a standardized protocol.1 Two tests were monitored by the same physician. The tests were made along a seldom traveled, flat, straight corridor (40 m long; marked every 1 m with cones to indicate turnaround points) with a hard surface. To minimize intraday variability, temperature effects, and biological rhythms, the 6-MWT was performed between 8 a.m. and 12 noon, a period characterized by a stable ambient temperature of 16–20 °C.24 All subjects performed the 6-MWT for the first time with no warm-up period and no encouragement. Subjects were told to avoid vigorous exercise in the 2 h prior to testing and to wear comfortable clothes and appropriate walking shoes.

The subjects sat in a chair located near the starting position for at least 10 min before the test started. During this time, dyspnea (visual analogue scale), HR and oxygen saturation (sat) (pulse oximeter, Nonin Medical, Inc., Minneapolis, MN, USA) and systolic and diastolic pressures (SP, DP, respectively) (sphygmomanometer, stethoscope Littmann ⁴⁶, Classic II S.E, Germany) were measured at rest (1). The test instructions to the subjects were those recommended by the ATS. At the end (2) of the 6-MWT, the same data, in addition to 6-MWD, were measured. HR was expressed as beats/min and as a percentage of predicted maximal HR [= 208 – 0.7 × age].25 In addition to 6-MWD (m), SP (mmHg) (SP₁, SP₂), DP (mmHg) (DP₁, DP₂), HR (HR₁, %HR₁, HR₂, %HR₂) and sat (sat₁, sat₂) were noted. As recommended,1 the second test began ~60 min after the first one, in order to reach similar HR₁.

Data analysis

The results of the 6-MWT having the highest 6-MWD were selected for statistical analysis. Preliminary descriptive analysis included frequencies for categorical variables and means ± SD for continuous ones.

Univariate and multiple regression analysis (influencing factors)

The dependent variable (6-MWD) was normally distributed. t-Tests were used to evaluate the associations between 6-MWD and categorical variables (gender, SL, SEL), and the Pearson product–moment correlation coefficients (r) evaluated the associations between 6-MWD and continuous measures [height, age, weight, BMI, parity, FEV₁ (l), FVC (l), PEF (l s⁻¹), SP₁, SP₂, DP₁, DP₂, HR (HR₁, %HR₁, HR₂, %HR₂) and sat (sat₁, sat₂)] and extreme obesity (BMI ≥ 40 kg/m²).20

The linearity of the association between the 6-MWD and the continuous measures was checked graphically by plotting each regressor against 6-MWD. Only significantly and linearly associated variables were entered into the model.

A linear regression model was used to evaluate the independent variables explaining the variance in 6-MWD. Candidate variables were stepped into the model with a stepwise selection method. To determine entry and removal from the model, significance levels of 0.15 and 0.05 were used, respectively. No colinearity between predictors was detected with variance inflation factors.

Effect of parity

An unpaired t-test and a χ² test were used to compare the 6-MWT data of the low parity vs. high parity groups.

Comparison with published regression equations

Measured 6-MWDs were compared with predicted distances calculated from the six published reference equations for the same age range as in the corresponding study, in several ways. As proposed by Bland and Altman,26 limits of agreement were used for comparison, with individual difference (measured minus predicted 6-MWD) plotted against the corresponding mean value. From these data,
limits of agreement were then calculated (mean difference between measured and predicted 6-MWD ± 1.96 SD). Finally, comparisons between measured and predicted values also included paired t-tests.

### 6-MWD reference equations

Reference equations were established using age, height, weight and gender as predictors of 6-MWD in another stepwise linear regression model. The models were evaluated by the correlation (r) and determination (r²) coefficients and the standard error (SE). The 95% confidence interval (95% CI) was calculated as follows: 95% Cl = 1.64 × residual standard deviation (RSD). A measured 6-MWD lower than the LLN (=theoretical value – 1.64 × RSD) was considered abnormal.

### Reliability of the simplified equation

The reliability of our simplified 6-MWD reference equation was evaluated in the second group of 30 healthy adults. A Bland and Altman technique compared the measured 6-MWD, the predicted distance derived from our simplified equation, and the predicted distance derived from the most satisfactory reference equations.

Analyses were carried out using SAS/UNIX statistical software (SAS version 9, SAS Institute, Cary, N.C.; proc freq, proc univariate, proc corr, proc reg). Significance was set at the 0.05 level.

### Results

An initial sample of 295 volunteer adults (160 women) was examined. Non-inclusion criteria, presented in detail in the Supplementary data, were found in 65 subjects.

### Demographic, anthropometric, spirometric and 6-MWT data

The anthropometric and spirometric data and activity scores of the included men (n = 104) were significantly different from those of the women (n = 125) (Table 1), except for BMI. One hundred and twenty-eight subjects (63 women) showed overweight and 55 (38 women) moderate obesity. One hundred and eighty-seven subjects (112 women) had a low physical activity score, 32 (11 women) had a moderate score, while 10 subjects (two women) had a high score.

The 6-MWT data are shown in Table 2 for women, men and the total sample. Wide 6-MWD ranges were noted for the entire group, from 345 to 761 m in women, and 476 to 893 m in men. The 6-MWD of the 125 women and the 104 men is shown in the Supplementary data (Fig. 1S), according to age, height and weight ranges.

### Univariate analysis

Gender significantly affected the 6-MWD (Table 2). On average, the 6-MWD values were 160 m greater in men when compared to women (p < 0.001). In the total sample, SL and SEL significantly affected the 6-MWD. On average, the 6-MWD values were 132 m and 30 m greater, respectively, in subjects having high SL (n = 130) compared to subjects having low SL (p < 0.001) and in subjects having high SEL (n = 146) compared to subjects having low SEL (p = 0.04).

### Multiple regression analysis: influencing factors

Table 3 presents the cumulative r² of the independent influencing factors included in the 6-MWD forward linear stepwise multiple regressions. Several factors did not independently explain the variability of 6-MWD, such as height, weight, BMI, FVC, FEV1, FEF, PEF, physical activity score and Hr1.

### Effect of parity

In the entire female population (n = 125), a negative univariate linear correlation was found between 6-MWD and parity (r = −0.39, p < 0.05). Parity also appeared to be a negative independent variable included in the forward linear stepwise multiple regression model for 6-MWD (Table 3). We found no correlation between parity and weight or BMI (p = 0.18, p = 0.58, respectively). The significant correlations between parity and age and height in this female population (r = 0.43, p < 0.05; r = −0.23, p < 0.05; respectively) could have reflected colinearity.

We thus analyzed two subgroups of women who differed only in parity (Table 4). In the 76 women from 45 to 59 years, we distinguished 38 women having low parity (3 ± 2) and 38 women having high parity (7 ± 1) with no significant age, anthropometric, spirometric, cardiovascular, or activity score differences (Table 4). In these women, no significant correlation was noted between parity and age, height, or BMI (r = 0.11, p = 0.32; r = 0.14, p = 0.23; r = 0.19, p = 0.09; respectively). 6-MWD was significantly lower in the high parity vs. low parity groups (589 ± 60 m vs. 555 ± 57 m, p = 0.01; respectively).

### Comparison with published regression equations

Fig. 1 shows, for the same age range, the Bland and Altman comparisons between measured 6-MWD and 6-MWD predicted from the published reference equations. There was a systematic bias between the measured and predicted values for most of these equations; that is to say, the difference with measured 6-MWD increased as the predicted 6-MWD increased. This was particularly evident for the equations from Camarri et al., Gibbons et al., and Chetta et al. (Fig. 1A, B and C, respectively). The correlation between mean differences and mean values was also significant for the
studies of Enright and Sherill\(^2\) (\(p < 0.001\), Fig. 1D) and Troosters et al.\(^3\) (\(p < 0.001\), Fig. 1E). Second, as can be deduced from Fig. 1, there was a difference between measured 6-MWD and 6-MWD predicted from these published reference equations, which was always statistically significant. Indeed, mean ± SD measured 6-MWD was slightly but significantly overestimated by 14 ± 65 m (\(p < 0.01\)), 35 ± 77 m (\(p < 0.01\)) and 78 ± 73 m (\(p < 0.01\)), respectively, with the reference equations from Troosters et al.\(^3\), Gibbons et al.\(^7\) and Camarri et al.\(^6\); and was significantly underestimated by 32 ± 65 m (\(p < 0.01\)), 72 ± 72 m (\(p < 0.01\)) and 90 ± 80 m (\(p < 0.01\)), respectively, with the reference equations from Poh et al.,\(^4\) Enright and Sherill\(^2\) and Chetta et al.\(^5\).

6-MWD simplified reference equations

Due to the inadequacy of the published equations, we established a reference equation adapted to our population based on the multiple regression analyses (Table 5). For practical, daily interpretation of 6-MWT, a reference equation should include only easily measured anthropometric data, so we established simplified equations with four common parameters: gender, age, height and weight. For women, men and the total sample, these parameters were significant independent predictors (Table 5). The single model for the total sample appeared to explain 77% of the 6-MWD variability. We thus used this simplified model as the reference equation for our population (Table 5).
Table 3  Independent variables included in the forward linear stepwise multiple regression model for the 6-min walk distance (6-MWD).

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>B</th>
<th>Cumulative $r^2$</th>
<th>SE</th>
<th>1.64 × RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women (n = 125)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>679.93</td>
<td></td>
<td>0.440</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>−3.52</td>
<td></td>
<td>0.488</td>
<td></td>
</tr>
<tr>
<td>Physical activity score</td>
<td>3.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SL (low:0/high:1)</td>
<td>13.06</td>
<td></td>
<td>0.514</td>
<td>60</td>
</tr>
<tr>
<td>SEL (low:0/high:1)</td>
<td>22.13</td>
<td></td>
<td>0.529</td>
<td></td>
</tr>
<tr>
<td>FEV$_1$ (l)</td>
<td>24.00</td>
<td></td>
<td>0.537</td>
<td></td>
</tr>
<tr>
<td>Parity (numerical)</td>
<td>−2.53</td>
<td></td>
<td>0.545</td>
<td></td>
</tr>
<tr>
<td><strong>Men (n = 104)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>1188.64</td>
<td></td>
<td>0.483</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>−5.32</td>
<td></td>
<td>0.483</td>
<td></td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>−6.28</td>
<td></td>
<td>0.533</td>
<td></td>
</tr>
<tr>
<td><strong>Total sample (n = 229)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>1051.58</td>
<td></td>
<td>0.549</td>
<td></td>
</tr>
<tr>
<td>FEV$_1$ (l)</td>
<td>12.49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (men:0/women:1)</td>
<td>−145.42</td>
<td></td>
<td>0.662</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>−4.58</td>
<td></td>
<td>0.743</td>
<td></td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>−5.27</td>
<td></td>
<td>0.770</td>
<td></td>
</tr>
<tr>
<td>Physical activity score</td>
<td>2.30</td>
<td></td>
<td>0.781</td>
<td></td>
</tr>
<tr>
<td>SEL (low:0/high:1)</td>
<td>12.78</td>
<td></td>
<td>0.783</td>
<td></td>
</tr>
</tbody>
</table>

SL: schooling level; SEL: socioeconomic level; FEV$_1$: forced expiratory volume in 1 s; BMI: body mass index; B: non-standardized regression coefficient; $r^2$: determination coefficient; SE: standard error; and RSD: residual standard deviation.

**Proposed model for the total sample:** 6-MWD (m) = 12.49 × FEV$_1$ − 145.42 × gender − 4.58 × age − 5.27 × BMI + 2.30 × physical activity score + 12.78 × SEL + 1051.58.

Reliability of the single simplified equation

The mean walking distance prospectively measured in 30 subjects (56 ± 11 yr, 1.63 ± 0.09 m and 75 ± 12 kg) was 640 ± 95 m, representing 102 ± 4% (range: 95–110%) of the predicted value calculated with our simplified equation reference. The difference between prospectively measured and predicted 6-MWD in these 30 subjects was not significant (8 ± 28 m, $p = 0.77$) and the correlation was significant ($r = 0.96$; $p < 0.01$).

Similar comparisons were made in these additional subjects between the prospectively measured 6-MWD and the corresponding data predicted from the most satisfying reference equations appearing in Fig. 1E and F. Fig. 2 shows the Bland and Altman graphic representations of these comparisons with the reference equation for North Africans (Fig. 2A) and the equations of Troosters et al. and Poh et al. As can be seen, the Troosters et al. reference equation (Fig. 2B) slightly but significantly overestimated our 6-MWD by 13 ± 38 m ($p < 0.05$) and the Poh et al. reference equation underestimated our 6-MWD by 44 ± 73 m ($p < 0.05$). In both cases, the limits of agreement were slightly but clearly greater than in our simplified equation.

Discussion

The 6-MWD of a large group of healthy North African adults older than 40 years was prospectively measured. This distance appeared to be influenced by anthropometric and spirometric data, physical activity score and SEL. Parity was also found to accelerate the 6-MWD decline. The published reference equations did not reliably predict 6-MWD in our population. Using gender, age, weight and height as independent predictors, we thus established a new single reference equation that explained 77% of the variability in the 6-MWD. Finally, in an additional group of adults prospectively assessed, our reference equation yielded satisfactory predictions.

6-MWT procedure

In a large group of healthy subjects with ages ranging from 40 to 85 years, we found the expected wide range in 6-MWD, in line with similar studies summarized in Table 2S (Supplementary data). The 6-MWT appeared to be mainly submaximal, as reflected by an HR$_2$ of 79 ± 13% of maximal predicted. Insofar as possible, we controlled the procedural factors that affect 6-MWT variability: respect of contraindications, clear information and preparation of subjects, schedule of test, choice of supervisor, supervision modalities, choice of corridor distance, absence of encouragement, and two tests performed. These methodological precautions thus allowed us to obtain reliable results.

Subject group composition

The sample size (n = 229) was within the range of most previous studies [sample size varying from 35 to 290].
Our recruitment mode and subject age range were similar to those of previous studies with comparable objectives (Table 2S). Ideally, reference values are calculated with equations derived from measurements observed in a representative sample of healthy subjects in a general population. Reference equations can also be derived from large groups of volunteers, provided that criteria for normal selection and proper distribution of anthropometric characteristics are satisfied. In order to minimize the voluntary and selection bias, all subjects were questioned so that any non-inclusion criteria would be detected. Our subjects were free from chronic disease, although 24% showed moderate obesity. We excluded underweight subjects and those with marked or extreme obesity, as did other authors. It is known that lung alteration occurs only in cases of marked obesity without recognized pulmonary disease. In addition, 32% of the general local population over 40 years shows moderate obesity, and our group composition reflected this “healthy” population. Therefore, the present study, which is the first in a North African population, provides results useful for the interpretation of 6-MWT in patients with chronic diseases living in this area.

### Table 4 Characteristics of women aged 45–59 years grouped according to parity (n = 76). (Parity ≤ 5) (n = 38) (Parity ≥ 6) (n = 38)

<table>
<thead>
<tr>
<th>Parity, anthropometric and spirometric data</th>
<th>(Parity ≤ 5) (n = 38)</th>
<th>(Parity ≥ 6) (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity (numerical)</td>
<td>3 ± 2</td>
<td>7 ± 1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>50 ± 4</td>
<td>52 ± 4</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.57 ± 0.06</td>
<td>1.58 ± 0.06</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69 ± 11</td>
<td>71 ± 10</td>
</tr>
<tr>
<td>BMI (kg m&lt;sup&gt;-2&lt;/sup&gt;)</td>
<td>28 ± 4</td>
<td>29 ± 3</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.80 ± 0.58</td>
<td>2.73 ± 0.54</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (l)</td>
<td>2.36 ± 0.40</td>
<td>2.33 ± 0.42</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC (absolute value)</td>
<td>0.85 ± 0.07</td>
<td>0.86 ± 0.06</td>
</tr>
<tr>
<td>FEF (l s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>2.81 ± 0.66</td>
<td>2.79 ± 0.75</td>
</tr>
<tr>
<td>PEF (l s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>5.26 ± 1.26</td>
<td>4.76 ± 1.16</td>
</tr>
</tbody>
</table>

| Activity scores                           |                       |                       |
| Household                                  | 2.32 ± 0.58           | 2.37 ± 0.43           |
| Sporting                                   | 2.74 ± 5.72           | 1.31 ± 2.72           |
| Leisure                                    | 1.08 ± 0.72           | 1.02 ± 0.90           |
| Physical                                   | 6.13 ± 5.85           | 4.70 ± 2.96           |

<table>
<thead>
<tr>
<th>Number (%) of women grouped according to parity and SL or SEL</th>
<th>(Parity ≤ 5) (n = 38)</th>
<th>(Parity ≥ 6) (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schooling level (SL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>20 (53%)</td>
<td>28 (74%)</td>
</tr>
<tr>
<td>High</td>
<td>18 (47%)</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>Socioeconomic level (SEL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>23 (61%)</td>
<td>28 (74%)</td>
</tr>
<tr>
<td>High</td>
<td>15 (39%)</td>
<td>10 (26%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6-MWT data</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>78 ± 8</td>
<td>127 ± 18</td>
<td>76 ± 9</td>
<td>122 ± 17</td>
</tr>
<tr>
<td>(% predicted)</td>
<td>45 ± 5</td>
<td>74 ± 11</td>
<td>44 ± 5</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>98 ± 1</td>
<td>98 ± 1</td>
<td>98 ± 1</td>
<td>98 ± 1</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>124 ± 15</td>
<td>157 ± 22</td>
<td>127 ± 16</td>
<td>160 ± 37</td>
</tr>
<tr>
<td>6-MWD (m)</td>
<td>589 ± 60</td>
<td>555 ± 57&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD. For abbreviations see Tables 1–3.<sup>a</sup> p < 0.05: parity ≤ 5 vs. parity ≥ 6.

Gender related difference in heart rate

In the present study, we found that resting Hr values were significantly lesser in women vs. men (Table 2). Our finding is different from previous studies showing gender related differences in Hr. However, compared to men of our study, only the subgroup of women aged between 50 and 70 years showed a statistical significant difference. Among our 125 women, 84 were menopausal (mean age of 59 years). Therefore, in the age range of 50–70 years, one explanation of the significant lower resting Hr could be the hormone replacement therapy (data not collected in our study), a therapy known to reduce Hr. End walking Hr values were also significantly lower in women (Table 2), unlike data from Chetta et al. study realized in subjects aged 20–50 years (Table 2S). In fact, our women of similar age range, walked the same 6-MWD than those of Chetta et al. by 124 m (767 ± 66 vs. 638 ± 44, respectively), explaining a higher end walking Hr by 38 beats/min (157 ± 18 vs. 122 ± 17 beats/min).
119 ± 18 beats/min, respectively). Therefore the difference in end walking Hr between the two studies, concerns only man groups, and is likely to be due to the level of exercise performed during the 6-MWT.

Influencing factors

The independent contributors to 6-MWD in our population sample were anthropometric and spirometric data, physical activity score and SEL (Table 3). A combination of some of these factors has been reported in studies from several countries, although with some study specificities (Table 2S). However, the combination of our independent variables was able to explain up to 78% of the variability in 6-MWD in our total sample, which is very satisfactory compared with previously published equations (Table 2S). Other factors that were not evaluated in the present study may nevertheless have influenced 6-MWD: lean body mass, diet habits, leg length and quadriceps force.3,4,33 We also found physical activity score to slightly but significantly contribute to the variability in 6-MWD. This result contrasts with those of Gibbons et al.,7 who found only a tendency towards difference between "active" and “sedentary” subjects. Other authors found no significant correlations between the 6-MWD and the scores of a daily activity questionnaire,3 self-reported physical activity including habitual walking,6 and regular physical activity.4 It should be underlined that our population was overall sedentary, with only a few very active subjects. Although physical activity has a favorable impact on aerobic fitness with aging,34 specific studies on the influence of regular and athletic activities on 6-MWD are still needed.

We found SEL to slightly but significantly contribute to the variability in 6-MWD. The effects of SEL on the spirometric variables are well documented in industrialized countries35,36: a low SEL accelerates their decline and is associated with small airway obstruction.36

Effect of parity

Parity significantly influenced the 6-MWT results, particularly in the subgroup of women between 45 and 59 years differing by low and high parity (Table 4). We attempted to avoid confounding factors by verifying that age, anthropometric, spirometric and cardiovascular data, activity scores, and SEL not differ between the groups (Table 4), and no colinearity was found. Therefore, high parity clearly appeared to cause a decline in the women’s submaximal aerobic fitness, as assessed by 6-MWD. In fact, for our entire female population within this wide age range, and for both men and women included in a single equation, parity was not entered into the final equation because of its relatively low
statistical influence. However, 6-MWD was lower by ~35 m in women of 45–59 years with high parity. These results may be clinically relevant when interpreting 6-MWT in women with chronic disease. A simple way to solve this problem would be to subtract 35 m from the LLN of these women. To our knowledge, the effects of repeated gestations on exercise tolerance, and particularly 6-MWD, have never been reported and should now be taken into account.

This phenomenon may reflect the general findings about aging and parity effects on health. Repeated gestations have been found to have potentially noxious effects on health, and several hypotheses have been advanced. First, hormonal alterations during pregnancy could generate aerobic system incapacity. As the 6-MWT solicits the aerobic system, repeated gestations may accentuate or prolong this incapacity. Biochemical modifications were also suggested, since increased oxidative stress has been found during pregnancy. With repeated gestations, the repeated oxidative stress could have negative effects on muscle function, explaining in part the 6-MWD declines with high parity. Last, impaired respiratory muscle function is associated with high parity, which may have influenced the ventilatory response in our subjects during exercise. The medical literature provides very little information on the influence of parity on exercise tolerance, however, and this may be a promising new direction for physiological and pathophysiological research, particularly for developing countries.

**Choice of the appropriate 6-MWD reference equation and interpretation**

We found significant and sometimes very large differences between measured 6-MWD and 6-MWD predicted from the published reference equations. The implications of this for adults with chronic diseases may be considerable and include potential errors regarding the level of patient disability and unrealistic expectations of interventions designed to improve 6-MWD. This argues for the use of our specific reference equation and confirms the ATS recommendation to continue establishing regional reference equations. The scientific societies recommend that reference equations be derived by valid and biologically meaningful statistical models, taking into account the dependence of the parameter studied with anthropometric data. For purely practical reasons, we established a single 6-MWD linear reference equation that included gender, height, age and weight as the independent variables. This equation still explained 77% of the 6-MWD variability, which is very satisfactory (Table 2).

Recently, Cote et al. prospectively followed 1379 COPD patients and tested the predictive value of the baseline 6-MWD according to American and European reference equations. They concluded that a value <350 m is associated with increased mortality and should

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**Table 5** Reference equation for the 6-min walk distance (6-MWD).

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>B</th>
<th>p-Level</th>
<th>$r^2$</th>
<th>SE</th>
<th>LLN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women (n = 125)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>397.40</td>
<td>&lt;0.01</td>
<td>0.52</td>
<td>153</td>
<td>–87</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>–4.99</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>–2.41</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>378.87</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men (n = 104)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>905.45</td>
<td>&lt;0.01</td>
<td>0.53</td>
<td>183</td>
<td>–92</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>–5.40</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>–2.22</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>171.60</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total sample (n = 229)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>720.50</td>
<td>&lt;0.01</td>
<td>0.77</td>
<td>122</td>
<td>–89</td>
</tr>
<tr>
<td>Gender (men:0/women:1)</td>
<td>–160.27</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>–5.14</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>–2.23</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>271.98</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For abbreviations see Table 3. $p$: probability; LLN: lower limit of normal.

6-MWD simplified reference equation $= -160.27 \times \text{gender} - 5.14 \times \text{age} - 2.23 \times \text{weight} + 271.98 \times \text{height} + 720.50$.

**Interpretation:** after the predicted 6-MWD value from this retained equation is computed for an individual subject, the LLN for that subject may be obtained by subtracting 89 m.

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**Figure 2** The Bland and Altman representation of measured and predicted 6-min walk distance (6-MWD) in 30 healthy subjects, with the reference equation for North Africans (Fig. 2A) and from Troosters et al. (Fig. 2B) and Poh et al. (Fig. 2C). Mean; mean ± 1.96 SD.
be regarded as abnormal. The present study supports these data as only one subject had a 6-MWD < 350 m.

Our additional prospective data confirmed the equation’s reliability and also illustrated the errors that could arise from using other equations in this population. Moreover, the LLN in our study could be obtained by subtracting 89 m from predicted 6-MWD, which was the lowest value compared with other studies (Table 2S). Therefore, given its high reliability, we propose that our simplified reference equation should be used in the North African population.

In conclusion, we established a reliable reference equation to interpret the results of 6-MWT in healthy North African adults. The 6-MWD can be easily predicted from simple parameters of gender, age, height, and weight. Our 6-MWD reference equation enriches the World Bank of reference equations, from which the physician should choose according to the patient’s locale and ethnic background.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

Ethics statement

The protocol was approved by our ethics committee, and written informed consent was obtained from each patient prior to the study.

Acknowledgment

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Supplementary material

The supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2008.07.023.

References


