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THE 6 MINUTE WALK DISTANCE IN HEALTHY SUBJECTS: REFERENCE STANDARDS FROM SEVEN COUNTRIES

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Abstract

Background: The six-minute walk distance (6MWD) predicted values have been derived from small cohorts mostly from single countries.

Objective: To investigate differences between countries and identify new reference values to improve 6MWD interpretation.

Methods: We studied 444 subjects (238 males) from 7 countries (10 centers) ranging from 40 to 80 years old. We measured the 6MWD, height, weight, spirometry,, heart rate (HR), the maximum HR during the 6MWT/the predicted maximum HR (%PredMaxHR), Borg dyspnea and oxygen saturation.

Results: The mean 6MWD was 571 (90) m (range 380-782). Males walked 30 m more than females ($p < 0.001$). A multiple regression model for the 6MWD included age, gender, height, weight, and %PredMaxHR (R^2_{adj}= 0.38, $p < 0.001$), but there was variability across centers (R^2_{adj}= 0.09-0.73) and its routine use is not recommended. Age had a great impact in 6MWD independent of the centers, declining significantly in the older population ($p < 0.001$). Age-specific reference standards 6MWD were constructed for male and female adults.

Conclusion: In healthy subjects, there are geographic variations in 6MWD and caution must be taken when using existing predictive equations. The present work provides new 6MWD standard curves that could be useful in the care of adult patients with chronic diseases.

Word count: 200

Key words: six minute walk test; healthy subjects; reference values; geographics variability.

Introduction

The 6-min walk test (6MWT) has gained importance in the assessment of functional exercise capacity in patients with chronic respiratory disease. It has proved to be reliable, inexpensive, safe and easy to apply (1-3). In addition, it correlates well with important outcomes including death (4-8).

Important differences in the distance walked have been observed in some studies performed in healthy subjects (9, 10). It is possible that differences in methodology and study populations could influence the results. Furthermore, most of the published predictive equations show a high variability in their predictive power suggesting that others factors usually not considered in the performance of the test could play an important role in the distance walked (9, 11-14).

The 6MWT guidelines were reported by the American Thoracic Society (ATS) seven years ago at a time when reference equations from healthy population-based samples were not available. The guidelines encouraged investigators to publish reference equations using these new guidelines (1). However, the series published until now have included a small number of individuals and from a single region (9-13). Currently, there are no universally accepted reference equations for clinical use and there is no available data from multicenter studies evaluating the possible regional differences of this test. We therefore conducted a cross sectional multicenter study in normal volunteers with age ranging from 40 to 80 years following the standardized approach provided by the ATS guideline.

Methods

Subjects

We prospectively studied 444 subjects (238 males) from 10 cities in 7 countries (Sao Paulo in Brazil, Santiago in Chile, Bogota in Colombia, Pamplona, Santa Cruz de Tenerife and Zaragoza in Spain, Montevideo in Uruguay, Boston and Tampa in the United States and Caracas in Venezuela) between November 2005 and May 2008. We attempted to balance the recruitment of subjects by gender, decades of age and centres. Most of the subjects included hospital workers and relatives of patients. They were included if they met the following criteria: 1) Age between 40-80 years; 2) No history of chronic disease that could influence their exercise capacity; 3) Active but not involved in any competitive sport. For the analysis of the relation between heart rate and 6MWD we excluded any subject on medications that could affect heart rate such as beta blockers or calcium channel blockers. All subjects gave informed consent to participate in the study and ethical committees from each site approved the study protocol.

Procedure

Smoking history and blood pressure were recorded. Weight and height were measured and used to calculate body mass index (BMI). Lung function was assessed by spirometry according to ATS/ERS guidelines (15). The presence and degree of co-morbidity was estimated using the Charlson index (16). We registered the medication taken by the patients. Subjects were questioned about involvement in regular self-reported physical activity in the previous three months. The subjects were classified as "active" (self reported physical activity:

lower extremities exercise for at least 30 minutes, ≥3 times per week) or "sedentary" (17).

6-Minute Walk Test

Two 6-minute walks test were performed following ATS guidelines (2). The evaluated parameters were the distance covered in 6-minute walk (6MWD) in meters and changes in oxygen saturation (SpO2) with exercise using a lightweight portable pulse oximeter. The longest 6MWD of two tests (performed the same day and separated at least by 20 minutes) was the primary outcome measure. To determine the effort made by the participants, we also registered heart rate (HR) during the test and determined the maximal HR. The predicted maximum HR (PredMaxHR) was derived from the formula MaxHR = 220 - Age.

Pre and post-6MWT dyspnea were measured using the Borg scale (18). Although all subjects performed the 6MWT according to the standard ATS guidelines, we determined the effort level using the ratio between the maximal HR during the test over the PredMaxHR (MaxHR/PredMaxHR).

Statistical analyses

Data are summarized as mean (SD) for normally distributed variables or median (5th–95th percentile) for those with non-normal distribution. Variables comparisons were performed using Student t or ANOVA with Bonferroni post-hoc tests, U Mann-Whitney or H Kruskal-Wallis tests and Pearson chi-squared test according to their type, distribution and number of the group involved in the comparisons. Correlations were estimated by Pearson´s or Spearman coefficients according type and distribution of variables. A forward stepwise multiple linear regression model was used to evaluate the predictive value of the different factors to explain the 6MWD. Centile charts were constructed using the 10th, 25th, 50th and 75th centiles of the best 6MMWD at ten years intervals for the male and female subjects. Significance level for all tests was established as a two tailed p-value ≤0.05. Calculations were made with SPSS 15.0 of SPSS Inc. ©, Chicago, Illinois, U.S.A.

Results

Subjects Characteristic

The cohort of 444 subjects was distributed as follows: 133 from Spain (40 from Tenerife; 66 from Zaragoza; 27 from Pamplona), 192 from South-America (40 from Uruguay; 26 from Venezuela; 39 from Colombia; 47 from Brazil; 40 from Chile) and 119 from USA (62 from Boston; 57 from Florida). The anthropomorphic and clinical characteristics are shown in Table 1. Most subjects were non obese (81%), non smoker (69%), frequently reported being active (71%) and had very few co-morbidities.

Six minute walk test (overall group)

None of the tests performed required to be interrupted and none of the individual required assistance during the 6MWT. The mean value for 6MWD was 571 (90) m, ranging from 380 to 782m. On average, the subjects walked 12 meters more in the second compared with the first test ($p < 0.001$). The second walk was longer in 69% of the subjects (Table 2). This difference was independent of gender (13m for male and 11m for female). The 6MWD was 30 m greater in men than in women [(585 (96) m) vs 555 (81) m, $p < 0.001$)]. The older subjects walked less than the younger: 40-49 yr: 611(85) m, 50-59 yr: 588 (91) m, 60-69 yr: 559 (80) m, 70-80 yr: 514 (71) m ($p < 0.001$). The effect of age on the 6MWD became significant above the age of sixty and this happened independent of gender (Figure 1).

The level of self reported physical activity of the subjects did not influence 6MWD ["active" 573 (92) m vs "sedentary" 568 (88) m, $p = 0.581$). Also, the presence of co-morbidities (Charlson ≥1) did not affect the walked distance [567 (85) vs 563 (87), $p = 0.719$]. Although the mean SpO_2 decreased during the test

(0.7%, $p < 0.001$), it was clinically irrelevant. Almost fifty percent of subjects increased their dyspnea score by ≥1 unit (Table 2).

The mean MaxHR/PredMaxHR was 73 (13)% and this variable showed a significant correlation with the 6MWD ($r = 0.34$, $p < 0.001$). One hundred and forty four volunteers (26% from Spain; 31% from South-America; 43% from USA) did not reach the 25th percentile (≥65%) of the MaxHR/PredMaxHR during the 6MWT. This group had some differences in comparison with the rest of the group (Table 2): They were younger [55 (42-70) vs 60 (42-77) years, $p < 0.001$)], had less co-morbidities (5% vs 17%, $p = 0.001$), but most importantly they walked a significantly lower distance [548 (78) m, $p < 0.001$].

Using linear stepwise multiple regression analysis, the best predictive equation for the 6MWD included age, height, weight, gender and MaxHR/PredMaxHR: 6MWD pred= 361 – (Age_{yr} x 4) + ($Height_{cm}$ x 2) + (MaxHR/PredMaxHR x 3) – ($Weight_{kg}$ x 1.5) – 30 (if women). This model accounted for 38% of the total variance of the 6MWD. Others variables, including FEV_1, dyspnea Borg scale did not show significant independent association with the 6MWD.

Six minute walk test (variability across centers)

The anthropometric characteristics by centers are shown in Table 3. There were not significant differences by age between centers and except the Florida population, the distributions of subjects were well balanced by gender. In addition, subjects from USA were taller and heavier. There were substantial differences in distance walked between countries (Figure 2): Brazilian subjects walked one hundred meters more than subjects from Venezuela or Chile; In Spain, subjects from Tenerife and Pamplona walked more than Zaragoza (Table 3). Although the MaxHR/PredMaxHR were higher in the centers with longer 6MWD (r: 0.908, p <0.0003;Table 3), these differences remained even if the effort was normalized by this factor: That is, progressive increases in achieved heart rate MaxHR/PredMaxHR (65%, 70% and 75%) were associated with longer distance walked in all centers but the differences among centers, remained significant (p <0.001).

The predictive equation had an important variability across the centers (R^2_{adj}= 0.09-0.73) and explained <30% of the 6MWD variance in four centers. In addition, not all of the variables had a predictive role in each center. Therefore, we could not obtain an adequate predictive equation for the population as a whole. However, age had a great impact in 6MWD in most of the centres and we rejected the equation. Therefore, we constructed an age-specific normative charts for male and female subjects from original 6MWD data (figure 1).

The clinical applicability of the curves here proposed is shown in figure 3, where the values reported from studies of different clinical conditions [pulmonary hypertension, congestive heart failure (CHF), interstitial pulmonary fibrosis and chronic obstructive pulmonary disease (COPD)] are plotted in the nomogram we constructed. The values for the 6MWD in those studies was clearly below the normal values in all of the reports and it was lower, the more severe the stage in CHF and COPD (7, 19-21).

Discussion

To our knowledge this is the first international multicenter study evaluating the geographic variations of 6MWD in a large cohort of healthy adults that performed the 6MWD following the ATS guidelines. There were two important findings. First, there were 6MWD geographic variations that cannot be explained by anthropometric factors even when the effort was adjusted using the heart rate (MaxHR/PredMaxHR ratio). Secondly the present work confirmed the importance of age and gender in the distance walked and proposes new reference standards curves for the use of 6MWD in clinical practice.

The 6MWT is used because it provides useful information of functional capacity in patients with cardio-respiratory diseases. In the last decade, six studies have evaluated the 6MWT in healthy adults in order to provide reference values for the 6MWD (3, 9-13). In two studies the population profiles were either too young or old (3, 13). In three other studies (10-12) the distance walked was very similar (approximately 600 meters) and much longer than the values reported in the largest cohort until now performed in the United States (9). The differences observed in these studies suggested the need to explore the factors responsible for the differences and to further standardize the test.

The first important finding in our study is the presence of differences between centres even following the same standardised 6MWD test. Differences across centers were large and could influence the results of studies conducted in different regions of the world. The possible reasons for these important variations are unlikely to be due to anthropometric factors because similar values were found across sites. If anything, subjects in the United States, where the values for walked distance was lower, were taller than those from the other regions. It is possible that the variability in 6MWD may be explained by inclusion of others factors such as speed of habitual walking or cultural aspects related to lifestyle, mood, attitude and motivation (subject and technician).

It could be argued that the intensity of the effort during the test played an important role in the differences found between centres. In fact, this argument could have been valid for some of the published results. Indeed, the age-predicted MaxHR were >75% in the studies with longer 6MWD (10, 11) whereas it was <65% in the cohort studied by Enright and Sherrill (9) who reported the shortest walking distance. We believe that our results indicate that the effort needs to be further standardized so that findings can be compared across studies. Indeed, in our cohort, analysis of the results from the patients in the lowest 25th percentile, showed that the increase in heart rate during the 6MWD was close to that reported by Enright and Sherrill (9) supporting the concept that lack of adequate effort may have influenced their results. However, lack of adequate effort can only partially explain our results because the differences by centers persisted in spite of controlling the effort by monitoring the heart rate. Our findings are in agreement with those reported in children, where the difference in heart rate before and after walk was an important clinical variable associated with the 6MWD (22). New studies in this area exploring the physiological variables and their response to this form of exercise are necessary (23, 24).

Our study also allowed us to evaluate the learning effect when two standardized tests are performed according to ATS guidelines (25). The results showed that the second test was on average 2% better than first test, although 27% of the subjects walked more in the first test. The difference between the first and second walk we observed was lower than the ones previously reported of 3 to 8% (10-12) and suggest a consistent methodology across centers.

The most important factor influencing the 6MWD in healthy subjects was age, a variable that has been observed in all previous studies with the exception of the one by Camarri et al (12). This is possibly related to the smaller sample size (70 subjects) and narrower age range (55-75 yr) of that study. The effect of age is more evident in patients older than sixty, independent of gender. Gibbons et al (11) had previously suggested that only older women had lower 6MWD. However, in that study there was a small number of subjects, which could explain the difference with our results. Also, our findings confirm previous studies that showed that the 6MWD is greater in male than females (3, 9-13), a fact also described in patients with COPD (26).

In addition to age and gender, we explored other possible factors that could influence the results of the 6MWD such as the post-walk Borg dyspnea, the self-reported physical activity, and the Charlson co-morbidity index. Although the post-walk Borg dyspnea scale has been recommended by the ATS guidelines (2), only one study has reported its value after the test. They did not observe any influence of dyspnea on the 6MWD, and this finding is supported by our results (13). The lack of effect of the self-reported physical activity on the 6MWD is consistent with other studies that also failed to demonstrate this association (10-12). However, it is possible that development of more sensitive physical activity scales could highlight some differences not detected with the instrument used in the current study. Overall, our subjects had a low co-morbidity index, a fact that could explain the little influence of this variable on the 6MWD. This contrasts to the findings reported in patients with COPD where co-morbidities have an important influence on the 6MWD (27).

About 60% of the variance in 6MWD remains unexplained by our model. This finding is consistent with most of the previous studies (3, 9, 11-13) except with that of Troosters et al who observed that age, height, weight and gender explained 66% of the variance in 6MWD in a small Belgian population (10).

In a novel approach, we provide reference percentile curves that could be useful in practice. As can be seen in figure 3, the reported absolute values from patients with different conditions known to affect functional capacity, are below the lower confidence interval of the calculated nomograms (7, 19-21), providing validity to the applicability of these curves. Although theoretically, an accurate predictive equation of reference value for comparison would be desirable, none of the equations has been sufficiently precise to provide such information. Further the absolute distance walked is a better predictor of mortality than that obtained from the application of corrective equations (8). In addition, the response of the distance walked to intervention is also best reported in absolute meters (28, 29) without corrections by predictive equations. The age specific nomograms for male and female here proposed can simplify the interpretation of individual results in clinical practice and trials and can provide graphic evidence of changes in values over time or after interventions.

The present study has some limitations. First, the sample of subjects in two cities (Caracas and Pamplona) was small, but differences were observed across other centers. Second, the participants were a not a random sample from the population of adults in each city. However, the subjects represented all age groups and balanced by gender. Third, the reference curves can´t be used in subjects younger than 40 years because they were not included. However, the 40-80 range is the age where most of the patients with cardio-pulmonary pathologies express their clinical disease. Finally, other potential variables not included in the present study could improve the variance explained by our predictive equations. Among them, psychological factors such as depression and anxiety, which have demonstrated some influence on exercise performance (14). Nevertheless, in our population, only 7 (2%) subjects reported depression and 12 individuals were taking related medications, a value that is much lower than the prevalence reported in studies including patients with chronic cardio-respiratory diseases. On the other hand, if we had included more variables, the model would be less simple, inefficient and more difficult to implement in clinical practice. As it stands, this study included all the factors that have shown a strong and independent association with the 6MWD.

In summary, for the first time, we report in a healthy population of both genders the existence of geographic differences in 6MWD that is independent of the standardisation technique. We propose new standard reference curves based on factors proven to have a significant impact on the 6MWD independent of the region of the world. These new 6MWD standards curves could be useful for the care of adult patients but further studies involving subjects from others populations and races will be needed for comparison.

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Table 1. Anthropometric and clinical characteristic of the subjects

	Value (n = 444 subjects)
Gender (M/F)*	238 / 206
Non-white Race*	23 (5%)
Age (yr)**	58 (42 – 76)
40-49 yr*	109 (24%)
50-59 yr*	129 (29%)
60-69 yr*	118 (27%)
70-80 yr*	88 (20%)
BMI (Kg/m^2)***	27 (4)
Smoking history (pack-yr)**	20 (5 - 52)
Active Smoker*	3%
Non Smoker*	69%
Sedentary Activity*	29%
Charlson ≥1*	12%

*Number and / or percent; **Median (5th-95th percentiles); ***Mean (SD)

Table 2. Cardiopulmonary parameters at rest and during the 6MWT.

	Value (n = 444 subjects)
FEV1 L*	2.78 (0.74)
FEV1%*	100 (14)
FVC%*	102 (14)
SpO2% at rest*	96.5 (1.7)
SpO2% post-6MWT*	95.8 (2.4)[a]
Respiratory Rate at rest*	16 (2)
Heart Rate (HR) at rest*	76 (10)
MaxH R / PredMaxHR*	73 (13)
End Dyspnea Borg**	0.5 (0-3)
Dyspnea Borg after 6MWT ≥1***	44%
6MWD (m) (1º test)*	554 (89)
6MWD (m) (2º test)*	565 (90)[b]
Best 6MWD (m)*	571 (90)

*Mean (SD); **Median (5^{th}-95^{th} percentiles); ***Number or percent.
a: SpO_2 decreased during the test (0.7%, $p < 0.001$).
b: The walked distance during the second was longer than the first test second (12 meters, $p < 0.001$).

Table 3. Anthropometric characteristic and 6MWD of the subjects by regions.

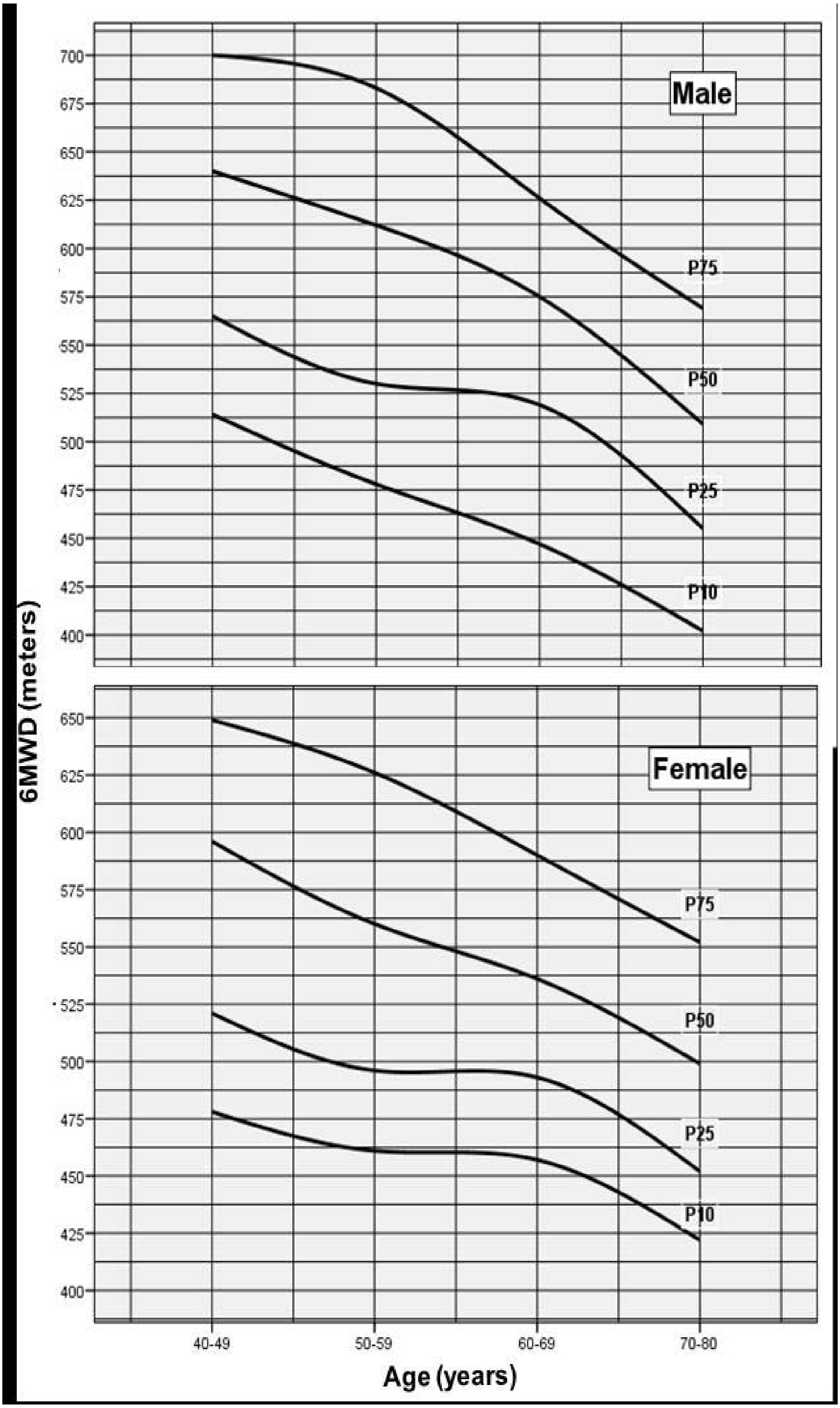
	Age (yr)*	**Gender (M / F)****	**Height (cm)*****	**Weight (Kg)*****	**MaxHR/ PredMaxHR (%)***; P_{10}**	**6MWD (m)*****
Tenerife (n=40)	57 (42 – 77)	20 / 20	163 (10)	74 (14)	81 (8); 71	613 (75)
Zaragoza (n=66)	55 (41 – 77)	34 / 32	165 (8)	71 (10)	63 (9); 53	510 (81)
Pamplona (n=27)	52 (40 - 77)	11 / 16	163 (8)	69 (12)	77 (10); 67	624 (73)
Montevideo (n=40)	59 (41 – 76)	20 / 20	165 (10)	73 (14)	75 (14); 60	590 (80)
Bogota (n=39)	59 (42 – 77)	19 / 20	159 (9)[b2]	66 (10)[c2]	88 (10)[d1]; 74	632 (63)
Caracas (n=26)	56 (42 – 71)	12 / 14	162 (8)	72 (13)	59 (12)[d2]; 44	510 (39)[e2]
Santiago de Chile (n=40)	60 (41 – 78)	20 / 20	164 (9)	70 (10)	76 (12); 60	550 (77)
Sao Paulo (n=47)	60 (40 – 80)	25 / 22	165 (10)	68 (12)	80 (12); 64	638 (95)[e1]
Florida (n = 57)	57 (41 – 74)	46 / 11[a]	173 (11)[b1]	87 (17)[c1]	64 (9); 53	535 (77)
Boston (n=62)	61 (47 – 75)	31 / 31	166 (10)	76 (16)	68 (9); 57	557 (87)
p-Value	0.111	0.014	<0.001	<0.001	<0.001	<0.001

*Median (5^{th}-95^{th} percentiles); **Number and / or percent; ***Mean (SD). P_{10} : 10^{th} percentile
M: male; F: female.
a: Only Florida had a different distribution by gender.
b1: Florida with Montevideo and Boston (p= 0.001) and others centers (p< 0.001).
b2: Bogota with Boston and Zaragoza.

c1: Florida with Boston ($p = 0.001$) and others centers ($p < 0.001$).
c2: Bogota with Boston ($p = 0.009$).
d1: Bogota with Tenerife (0.058), Sao Paulo ($p = 0.006$), Pamplona ($p = 0.001$) and the rest of the centers ($p < 0.001$).
d2: Caracas with all the centers ($p < 0.001$) except Boston ($p = 0.043$) and no statistical differences with Zaragoza and Florida.
e1: Sao Paulo with Zaragoza, Caracas, Santiago de Chile, Florida and Boston ($p < 0.001$). No significant differences with other centers.
e2: Caracas with Tenerife, Bogota and Sao Paulo ($p < 0.001$); with Montevideo ($p = 0.003$) and no statistical difference with Zaragoza. Santiago de Chile, Florida and Boston.

Figure Legends.

Figure 1. Reference curves based on age and divided in percentiles of 6 minute walked distance (6MWD) in normal men and women.



Male
Female
P75
P50
P25
P10
700
675
650
625
600
575
550
525
500
475
450
425
400
6MWD (meters)
40-49
50-59
60-69
70-80
Age (years)

Figure 2. Histogram of the 6 minute walk distance (6MWD) in the different centers.

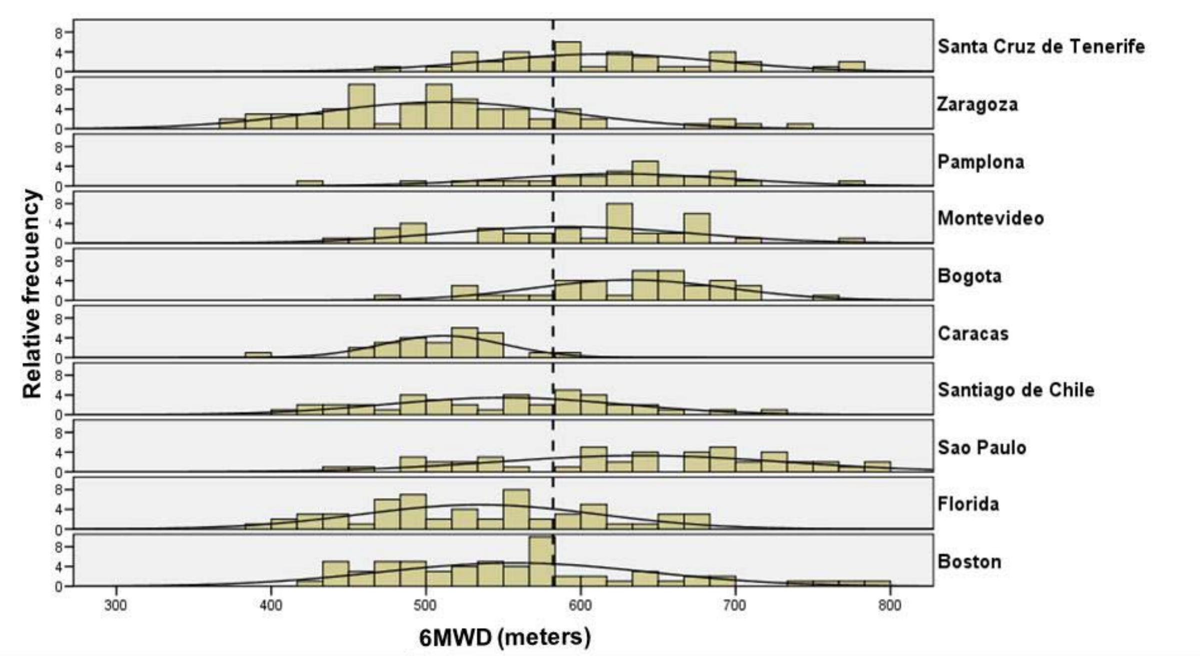
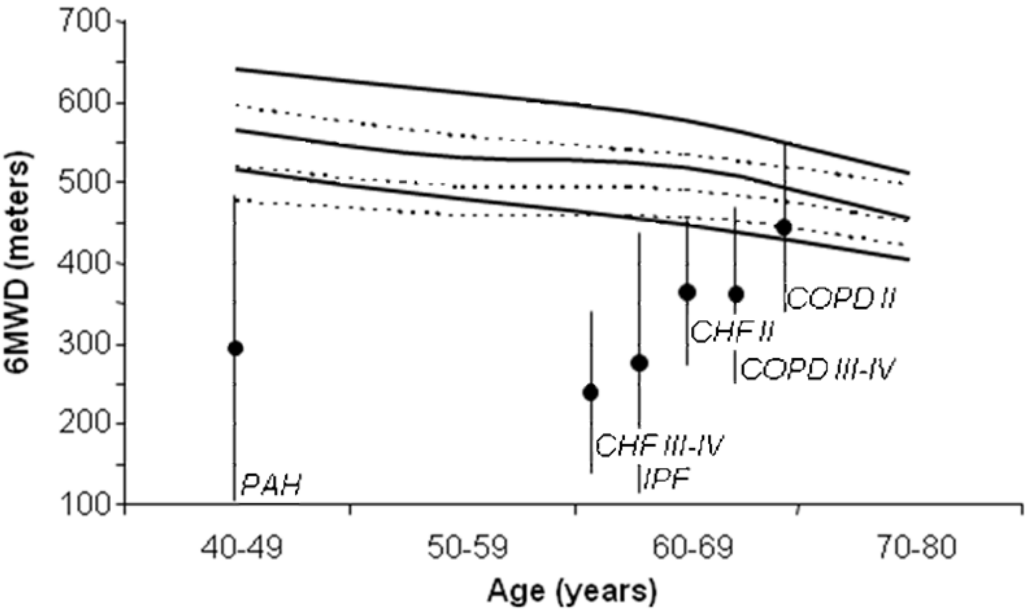


Figure 3. Percentiles (10, 25 and 50) curves for 6MWD (continuous line = male, dashed line = females) compared with the published data of the 6MWD for several important chronic diseases [Primary Pulmonary Hypertension (HPA, ref. 19), Idiopathic Pulmonary Fibrosis (IPF, ref. 20), Congestive Heart Failure subdivided according to the NYHA classification (CHF, ref. 21) and Chronic Obstructive Pulmonary Disease subdivided according to GOLD (COPD, ref. 7)].



6MWD (meters)
700
600
500
400
300
200
100
Age (years)
40-49
50-59
60-69
70-80
PAH
CHF III-IV
IPF
CHF II
COPD III-IV
COPD II