Gait-speed and oxygen flow during six-minute walk test predicts mortality in patients with advanced lung disease

Irina Timofte1, Adriano Tonelli2, Montserrat Diaz-Abad1, Avelino Verceles1, Nicholas Ladikos3, Aldo Iacono4, Michael L. Terrin5, Marniker Wijesinha6, Olufemi Akindipe2, Maher Baz7

1Department of Medicine, Division of Pulmonary and Critical Care, University of Maryland School of Medicine, Baltimore, MD; 2Department of Pulmonary and Critical Care, Respiratory Institute, Cleveland Clinic, Cleveland, OH; 3Department of Pharmacy, Johns Hopkins Medicine/Suburban Hospital, Bethesda, MD; 4Department of Pulmonary and Critical Care, University of Maryland School of Medicine, Baltimore, MD; 5Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD; 6Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD; 7Department of Lung Transplantation, University of Kentucky, Lexington, KY, USA

Abstract

The six-minute walk test (6MWT) is a useful tool to predict outcomes in patients with advanced lung diseases. Greater distance walked has been shown to have independent prognostic value. We reviewed the medical records of 164 patients with advanced lung disease who underwent lung transplant evaluation. Results of the 6MWT (distance walked, oxygen required to maintain oxygen saturation >90%, and gait speed) were recorded and analyzed with respect to mortality. 6MWT mean oxygen (O2) flow via nasal cannula was 3.5±3.7 L/min. The distance walked in meters (m) and percent predicted distance were inversely associated with mortality, hazard ratio (HR): 0.995 per meter (95% CI 0.992-0.998) for walk distance in meters and 0.970 per % predicted distance (95% CI 0.990-0.999). Patients who walked <200 meters [HR: 2.1 (95% CI 1.1-4.0)] or <45% of predicted, HR: 2.7 (95% CI 1.2-5.7) had higher mortality. O2 flow during the test had a direct association with mortality (HR: 1.1 per L/min (95% CI 1.0-1.2). In multivariate analysis, O2 flow >3.5 L/min remained predictive of mortality, HR: 1.1 per L/min (95% CI 1.0-1.2). Gait speed was higher in patients who survived through follow-up compared to patients who died (mean 0.83±0.35 m/s vs 0.69±0.33 m/s, p=0.03). Gait speed >0.8 m/s was a predictor of survival, HR 3.4 (1.1, 10.6). In summary, distance walked and O2 flow during the 6MWT were predictors of mortality in patients with advanced lung disease. Patients who required more than 3.5 L/min of O2 to maintain oxygen saturation >90% had a higher mortality. Faster gait speed during the 6MWT was also associated with better survival.

Introduction

The six-minute walk test (6MWT) is a simple functional test used in clinical practice and research for the assessment of exercise capacity in patients with moderate-to-severe cardiopulmonary disease. Since first being introduced by Butland in 1982 [1], this test has been particularly useful in assessing patients with chronic obstructive pulmonary disease (COPD) [2-4], pulmonary hypertension [5], interstitial lung disease [6], cystic fibrosis [7] and post-acute respiratory distress syndrome [8]. Lung transplantation is a therapeutic option for a broad spectrum of chronic, incapacitating pulmonary disease. The distance walked during the 6MWT is an important factor in guiding decisions about the time for lung transplant listing. More than three decades ago, Kadíkar et al. showed that a 6MWT distance <400 meters was valuable in listing for lung transplantation [9]. Subsequently, the
6MWT distance was incorporated in the calculation of the lung allocation score [10]. But, there are few disease-specific predictors to guide listing [11].

In patients with chronic lung diseases gait speeds reflect the overall level of impairment and offers an integrated index of physical activity. There are limited data regarding the importance of gait speed and oxygenation saturation during 6MWT in lung transplant evaluation.

We hypothesized that 6MWT walked distance, gait speed, and/or oxygen flow requirements are prognostic for patients with advanced lung disease evaluated for lung transplantation. The purpose of the study is to assess these in predicting mortality among advanced lung disease patients.

### Materials and Methods

This study was a retrospective review of the records of 164 patients who underwent lung transplant evaluation at the University of Florida between March 2001 and November 2008. Lung transplant evaluation consisted of history, physical examination, laboratory testing, chest X-ray imaging, pulmonary function tests, 6MWT, electrocardiogram, right heart catheterization and interviews with social and psychology services. We searched the U.S. Social Security Death Index for vital status outcomes. This study was approved by the University of Florida IRB.

### Six-minute walk test

We recorded the data from each subject first, 6MWT performed as part of the initial lung transplant evaluation according to the American Thoracic Society guidelines [12]. The tests were supervised by respiratory therapists with patients on the same supplemental oxygen as the patients were using at home unless the baseline pulse oximetry (SpO2) measurement was <90 %, for which oxygen flow was increased by 1 l/min every min until SpO2 ≥90% was achieved.

Patients were instructed to walk the corridor from one end to the other, as many laps as comfortable within the permitted time. Tests were stopped at six min or earlier for chest pain, intolerable dyspnea, gait instability, or other signs of severe distress [12]. In addition to the total distance walked, the oxygen flow required to keep a SpO2 ≥90% was recorded. Before, during and immediately after the test, heart rate, blood pressure, SpO2 and Borg dyspnea scale were documented. Blood pressure was measured using an automated blood pressure monitor; heart rate was determined by a reliable waveform on pulse oximeter. The following formulas were used to predict walk distance for a calculation of percentage of predicted; for men, 6MWD = (7.57 x height(cm)) - (5.02 x age) - (1.76 x weight(kg)) - (5.78 x age) - 309 m; and for women, 6MWD = (2.11 x height(cm)) - (2.29 x weight(kg)) - (5.78 x age) - 667 m [9].

### Gait speed

The gait speed data were obtained from the data measured during the 6MWT. Gait speed was calculated for each participant using total distance (m) walked divided by total time walked in seconds.

### Outcome variables

The outcome is mortality. Data regarding lung transplant listing, transplantation, and survival were obtained from a lung transplant database maintained by the institution and medical records. The U.S. Social Security Death Index [13] was queried when needed to confirm decease.

### Statistical analysis

Continuous data are reported as mean ± standard deviation (SD). Chi-square and Student’s t-test were used to compare categorical and continuous variables, respectively. Survival from the date of 6MWT was analyzed, censored at the time of transplant and was analyzed according to the method of Kaplan-Meier. Survivors, awaiting lung transplantation, were censored at the end of the study (03/13/2009). Univariate analysis was performed and multivariate analyses adjusted for age, gender and underlying disease (obstructive versus restrictive) were performed using Cox regression and expressed as hazard ratio (HR) with 95% confidence interval (CI). 6MWT distances were assessed as discriminator values using receiver operating characteristic (ROC) curves, with mortality as the dependent variable. Similar ROC analyses were performed for gait speed and oxygen flow used during the 6MWT. Maximum follow-up time was 8 years. All p values reported are two tailed. A p-value ≤0.05 was considered significant. The analyses were performed using the statistical packages SPSS, version 17 (SPSS Inc., Chicago, IL, USA) and SAS Software, version 9.4.

### Results

#### Patient’s initial characteristics

A total of 164 patients underwent lung transplant evaluation, age 51.8±0.9 years and 58% women. Underlying diagnoses included COPD (33%), idiopathic pulmonary fibrosis (22%), cystic fibrosis (11%), pulmonary fibrosis related to connective tissue disease (11%), sarcoidosis (7%), alpha-1 antitrypsin deficiency (6%), pulmonary arterial hypertension (4%), and others (6%). Most patients had airflow obstruction (54%) on spirometry. Right heart catheterization revealed mean pulmonary artery pressure 29.4±19.7 mm Hg, cardiac output 4.97±1.3 l/min. Patient characteristics are presented in Table 1.

#### 6MWT results

During the 6MWT a mean of 3.5±3.7 l/min of O2 flow was required by the cohort to complete the test. The average 6MWD was 261±123 m, 44±21 % of predicted. Even with increasing O2 flow, mean SpO2 dropped 6.8±5.6 % from the beginning to the end of evaluation and heart rate increased 21±13 bpm during the test (Table 1).

#### 6MWT parameters and survival

Survival probability (transplantation censored) from the time of initial 6MWT was 89% and 59% at one and five years, respec-
tively. The distance walked and percent of predicted distance were associated inversely with mortality - HR: 0.995 per meter (95% CI 0.992-0.998) for walk distance in meters and 0.970 per % predicted distance (95% CI 0.950-0.990). Mortality was increased for patients who walked <200 m (HR: 2.1, 95% CI: 1.1-4.0) or <45% of predicted walk distance (HR: 2.7, 95% CI: 1.2-5.7). The distance walked was analyzed by receiver operating characteristic (ROC) (Figure 1). The area under the curve was 0.7 (95% CI 0.6-0.8, p=0.001). The O2 flow (l/min) during the test had a direct association with mortality (HR: 1.1 for O2 flow per l/min (95% CI 1.02-1.2)). The area under the curve for the oxygen flow was 0.6 per l/min (95% CI 0.99-1.19, p=0.06). There was no association between the difference in heart rate or SpO2 before and at the end of exercise and mortality. In multivariate analysis only the O2 flow predicted mortality (HR: 1.1 for O2 flow per l/min; 95% CI: 1.01-1.2). Patients who required >3.5 O2 l/min had a higher one year and five-year mortality.

**Gait speed results**

Mean gait speed was 0.79 m/sec (SD 0.34). Details regarding gait speed are presented in Table 2. The histogram comparing the distribution of gait speed in patients who survived with patients who did not survived is presented in Figure 3 (p=0.01). Survival was associated with faster gait speed (mean 0.8±0.35 m/s vs 0.7±0.33 m/sec; p=0.03). The area under the curve for

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**Table 1. Patient characteristics at baseline.**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>O2 in l/m</th>
<th>O2 in l/m</th>
<th>p-value</th>
<th>Slow gait speed</th>
<th>Fast gait speed</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n=164</td>
<td>n=94</td>
<td>n=68</td>
<td></td>
<td>n=87</td>
<td>n=77</td>
<td></td>
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<td><strong>Demographics</strong></td>
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</tr>
<tr>
<td>Age, years</td>
<td>Mean (SD)</td>
<td>52(11.9)</td>
<td>50 (13)</td>
<td>54 (9)</td>
<td>0.05</td>
<td>54 (10.3)</td>
<td>50(13.4)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female (%)</td>
<td>94 (57%)</td>
<td>50 (53%)</td>
<td>44 (65%)</td>
<td></td>
<td>50 (57%)</td>
<td>44 (57%)</td>
</tr>
<tr>
<td><strong>Pulmonary function and six-minute walk test</strong></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Forced vital capacity percent of predicted</td>
<td>Mean (SD)</td>
<td>46(14)</td>
<td>46(13)</td>
<td>46 (15)</td>
<td>0.92</td>
<td>47 (14)</td>
<td>46 (13)</td>
</tr>
<tr>
<td>Forced expiratory volume percent of predicted</td>
<td>Mean (SD)</td>
<td>35(19)</td>
<td>33(18)</td>
<td>38(20)</td>
<td>0.15</td>
<td>32 (19)</td>
<td>39 (19)</td>
</tr>
<tr>
<td>Total lung capacity</td>
<td>Mean (SD)</td>
<td>90 (43)</td>
<td>97 (44)</td>
<td>81(37)</td>
<td>0.02</td>
<td>100.2 (41)</td>
<td>78(38)</td>
</tr>
<tr>
<td>Diffusion capacity for carbon monoxide</td>
<td>Mean (SD)</td>
<td>32 (19)</td>
<td>34 (20)</td>
<td>29 (14)</td>
<td>0.1</td>
<td>27 (15)</td>
<td>39 (20)</td>
</tr>
<tr>
<td>6-minute walk distance, meter</td>
<td>Mean (SD)</td>
<td>263 (123)</td>
<td>283 (132)</td>
<td>231 (102)</td>
<td>0.005</td>
<td>181.4 (74)</td>
<td>356 (100)</td>
</tr>
<tr>
<td>6MWD &lt;200 meter</td>
<td>Nr (%)</td>
<td>65 (40%)</td>
<td>34 (36%)</td>
<td>31 (45%)</td>
<td>0.22</td>
<td>57 (66%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>Mean (SD)</td>
<td>4.9 (1.3)</td>
<td>5.0 (1.2)</td>
<td>4.9 (1.4)</td>
<td>0.41</td>
<td>4.8 (1.1)</td>
<td>5.1 (1.4)</td>
</tr>
<tr>
<td>Mean pulmonary Artery pressure mmhg</td>
<td>Mean (SD)</td>
<td>20 (1)</td>
<td>27 (8)</td>
<td>32 (12)</td>
<td>0.02</td>
<td>30 (10)</td>
<td>28 (9.5)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Mean (SD)</td>
<td>57 (8.5)</td>
<td>58 (6.8)</td>
<td>57(10.3)</td>
<td>0.34</td>
<td>57 (8.7)</td>
<td>58(8.2)</td>
</tr>
<tr>
<td><strong>Transplant characteristics</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying disease (obstructive vs restrictive)</td>
<td>Obstructive (%)</td>
<td>88(53%)</td>
<td>57 (60%)</td>
<td>31 (45%)</td>
<td>0.27</td>
<td>55 (63%)</td>
<td>34 (38%)</td>
</tr>
<tr>
<td>Patient underwent transplant</td>
<td>Transplanted (%)</td>
<td>48(29%)</td>
<td>31 (53%)</td>
<td>17 (25%)</td>
<td>0.27</td>
<td>22 (25%)</td>
<td>27 (35%)</td>
</tr>
<tr>
<td>Patient died before transplant</td>
<td>Died (%)</td>
<td>31 (19%)</td>
<td>15 (16%)</td>
<td>16 (24%)</td>
<td>0.22</td>
<td>22 (25%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Type of lung transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single (%)</td>
<td>23 (14%)</td>
<td>18 (58%)</td>
<td>5 (29%)</td>
<td>0.06</td>
<td>8 (38%)</td>
<td>15 (64%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Double (%)</td>
<td>25 (15%)</td>
<td>13 (42%)</td>
<td>12 (70%)</td>
<td>14 (63%)</td>
<td>11 (41%)</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. 6MWT distance Receiver operating characteristic (ROC) curve with mortality as outcome. AUC, area under the curve; CI, confidence interval.
dichotomized gait speed receiver operating characteristics (Figure 4) was 0.65 (95% CI 0.052-0.68, p=0.01).

**Patient’s outcomes**

Twenty-nine (29) % of patients underwent lung transplantation of which 23 (14%) underwent single and 25 (15%) underwent double lung transplantation; 19% of patients died before lung transplantation.

The Kaplan-Meier plot displaying the survival censoring transplant for the full cohort is shown in Figure 5. The estimated survival at 5 years was 56% for the overall cohort. A Kaplan-Meier plot comparing the survival censoring transplant between the patients with fast gait speed (>0.8 m/min) and slow gait speed (≤0.8 m/min) is shown in Figure 6, at 5 years 65% in the fast gait speed and 49 % in the slow gait speed group.

**Discussion**

In the present study of patients with heterogeneous advanced lung diseases evaluated for lung transplantation, we found that the amount of oxygen required to maintain SpO₂ ≥90%, distance walked during 6MWT, and gait speed were associated with mortality. A distance of <200 m predicted increased mortality. In multivariate analysis baseline O₂ flow (>3.5 L/min) to maintain O₂ saturation >90% was an independent predictor of mortality.

Since the first successful human lung transplant in 1983, there have been increasing numbers of lung transplants performed every year. However, the list of potential candidates for lung transplantation exceeds the number of donors. Also, there is a critical balance between transplanting patients too early or too late. In an effort to direct lung transplantation to more urgently ill patients, the lung allocation score (LAS) system was implemented in 2005 and dramatically altered the way in which donor lungs were allocated in the United States. There has been a decrease in mortality on the wait list since 2005 [11,14,15].

Previous studies showed that 6MWD is an independent predictor of all-cause as well as pulmonary-related mortality. COPD patients who walked <300 m had a significantly greater mortality rate [16]. In patients with idiopathic pulmonary arterial hypertension (IPAH), 6MWD <300 m was associated with increased mortality [17]. In patients with idiopathic pulmonary fibrosis, 6MWD <200 m was associated with mortality [18], results similar to our study. Castleberry et al. reported the association between the 6MWD and survival after lung transplantation [19]. In his study, 6MWD is significantly associated with post-transplant survival.

**Table 2. Gait speed characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>All patients n=164</th>
<th>Slow gait speed n=87</th>
<th>Fast gait speed n=77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait speed</td>
<td>Mean (SD)</td>
<td>0.79 (0.34)</td>
<td>0.54 (0.17)</td>
</tr>
<tr>
<td>Patient underwent transplant</td>
<td>Transplanted (%)</td>
<td>48 (29%)</td>
<td>22 (25%)</td>
</tr>
<tr>
<td>Patient died before transplant</td>
<td>Died (%)</td>
<td>31 (19%)</td>
<td>22 (25%)</td>
</tr>
</tbody>
</table>
and increasing 6MWD was associated with significantly lower overall hazard of death.

In the present study we also have shown that the maximum O2 flow used during the 6MWT had a significant association with mortality. Patients who required >3.5 O2 l/min to maintain O2 saturation>90%, had reduced 1-year and the 5-year survival. Although mortality is related to use of oxygen therapy in patients with COPD [4], for patients with sarcoidosis awaiting lung transplantation [20] or patients with idiopathic pulmonary fibrosis complicated by pulmonary arterial hypertension [21], no specific cut off for O2 flow is documented in the literature. The prognostic value of O2 flow during 6MWT to maintain O2 saturation >90% is a new predictor of mortality in patients with advanced lung disease undergoing lung transplant evaluation.

A recent article demonstrated that gait speed is independently associated with 6MWD in patients with severe chronic lung disease [22]. For COPD patients, gait speed had a strong correlation with pulmonary function, functional capacity, and health-related quality of life [23-25]. Though gait speed has been shown to predict survival in older adults [26], the association between gait speed and survival in patients with severe lung disease evaluated for lung transplantation has not been thoroughly evaluated. Our study demonstrates that gait speed predicts mortality in patients with advanced lung disease.

We are interested in gait speed because it is a simple method for patient testing, largely independent of time and setting. Our study shows that faster gait speed is associated with better survival and could substitute for the 6MWT.

The study has limitations associated with the retrospective nature of our database. Data regarding dyspnea and muscle fatigue at the end of the test are not included in our database; therefore, those outcomes were not analyzed. Although a previous study showed that decreases in SpO2 during exercise has prognostic value [18], our design did not allow us to demonstrate an association between the change in SpO2 before and at the end of exercise and mortality. A relatively small sample size in a single center cohort limits our generalizability.
Conclusions

Our study showed that oxygen flow to maintain O₂ saturation >90% during a 6MWT predicted mortality in a cohort of advanced lung disease patients evaluated for lung transplantation and may be valuable for predicting wait list mortality. Faster gait speed is associated with better survival.

References