COPD: Journal of Chronic Obstructive Pulmonary Disease ›

Volume 5, 2008 - Issue 2

Free access

ORIGINAL RESEARCH

Exercise Testing in Severe Emphysema: Association with Quality of Life and Lung Function

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Pages 117-124 | Published online: 02 Jul 2009

Cite this article https://doi.org/10.1080/15412550801941265

Abstract

Six-minute walk testing (6MWT) and cardiopulmonary exercise testing (CPX) are used to evaluate impairment in emphysema. However, the extent of impairment in these tests as well as the correlation of these tests with each other and lung function in advanced emphysema is not well characterized. During screening for the National Emphysema Treatment Trial, maximum ergometer CPX and 6MWT were performed in 1,218 individuals with severe COPD with an average FEV_1 of 26.9 ± 7.1 % predicted. Predicted values for 6MWT and CPX were calculated from reference equations. Correlation coefficients and multivariable regression models were used to determine the association between lung function, quality of life (QOL) scores, and exercise measures. The two forms of exercise testing were correlated with each other (r = 0.57,

6MWT (27.6 ± 16.8 vs. 67.9 ± 18.9 % predicted). Both exercise tests had similar correlation with measures of QOL, but maximum exercise capacity was better correlated with lung function measures than 6-minute walk distance. After adjustment, 6MWD had a slightly greater association with total SGRQ score than maximal exercise (effect size 0.37 ± 0.04 vs. 0.25 ± 0.03 %predicted/unit). Despite advanced emphysema, patients are able to maintain 6MWD to a greater degree than maximum exercise capacity. Moreover, the 6MWT may be a better test of functional capacity given its greater association with QOL measures whereas CPX is a better test of physiologic impairment.

Key words: :

Emphysema | Lung diseases | obstructive | Exercise tests | Quality of life | Clinical trial | multicenter studies

INTRODUCTION

The 6-minute walk test (6MWT) measures the distance that an individual can walk in 6 minutes (6-minute walk distance, 6MWD) and was designed as a submaximal exercise test to reflect functional impairment in patients with lung disease ([1]). Currently it is widely used in clinical trials as a functional outcome as well as a predictor of mortality ([2], [3]). The advantages of the 6MWT include the use of minimal technical resources and employment of a familiar form of exercise. In contrast, cardiopulmonary exercise testing (CPX) is used to measure maximum physiologic exercise performance and provides specific measurements of cardiac and pulmonary performance such as maximum oxygen consumption, ventilation and estimates of cardiac output ([4]).

Compared to the 6MWT, CPX employs a standardized workload and is less subject to learning effects ([4]). It requires more advanced technology and is most often performed on a bicycle ergometer which employs a less familiar task than walking. Choice of exercise testing in chronic obstructive pulmonary disease (COPD) is controversial. While CPX provides more definitive measures of the physiology of exercise, some experts argue that the 6MWD provides a better assessment of

In general, measures of lung function have limited ability to predict exercise capacity in an individual. The forced expiratory volume in 1 second (FEV_1) is the most widely used lung function measurement to determine disease severity in COPD. However, a limitation of the FEV_1 is that it does not directly reflect the degree of static and dynamic hyperinflation in an individual with COPD. Recently, the development of dynamic hyperinflation with an increase in end-expiratory lung volume has been correlated with exercise limitation due to dyspnea ([7], [8], [9]). As inspiratory capacity (IC) is inversely related to end-expiratory lung volume, it is useful as a marker for lung hyperinflation. Reduced IC and IC/TLC ratio have been associated with poorer exercise performance and survival in COPD ([7], [10], [11]). Because of its relationship with dynamic hyperinflation, IC might be a better predictor of maximal exercise performance in COPD than FEV_1, but it is not known whether IC is a useful predictor of performance of the six-minute walk test.

The National Emphysema Treatment Trial (NETT) was a multicenter clinical trial comparing lung volume reduction surgery to medical treatment in individuals with advanced emphysema ([12]). During a comprehensive baseline evaluation, participants performed both 6MWT and CPX along with measures of lung function and quality of life. Using physiologic data collected during screening for the NETT, we compared these two types of exercise tests in individuals with advanced emphysema to determine the degree of impairment in CPX and 6MWT. In addition, we hypothesized that the CPX had a better correlation with lung function measurements while 6MWT would correlate better with quality of life scores. Finally, we wanted to know whether lung function measurements, including inspiratory capacity, were similarly correlated with both forms of exercise tests.

METHODS

Participants

Participants were enrolled in the National Emphysema Treatment Trial, a randomized multicenter clinical trial comparing lung volume reduction surgery plus medical treatment to medical treatment alone for advanced emphysema ([12]) Eligibility criteria included radiographic evidence of emphysema, FEV_1 45% predicted or less, total lung capacity (TLC) at least 100% predicted, residual volume (RV) at least 150% predicted

smoking for four months prior to baseline screening and be free from severe co-morbid conditions. The trial design and main results have been previously published ([12], [13]). The research protocol was approved by the Institutional Review Boards of all participating institutions, and informed consent was obtained from participants prior to randomization.

Procedures

During the baseline evaluation and prior to initiation of pulmonary rehabilitation and randomization, participants performed a 6MWT and a maximum cycle ergometry exercise test within a 6-week period. Prior to the 6MWT, a treadmill test at 1-2 mph was performed to determine supplemental oxygen requirements during testing. The 6MWT was performed using a standard protocol using scripted prompts at 1-minute intervals. If oxygen supplementation was required during testing, a staff member walked behind the participant to carry the oxygen. Course layout and length varied by participating institution. Maximum walking distance, expressed as a percent predicted ([14]), was used for analysis.

Maximum symptom-limited CPX was performed on a bicycle ergometer with an increase in workload of either a 5 or 10 Watts at 1-minute intervals, based on the participant's maximum voluntary ventilation. Participants breathed 30% oxygen during the test in order to limit hypoxemia as a cause of exercise limitation. Maximum exercise, expressed as percent of predicted ([15]), was used for analysis.

Pulmonary function testing was performed in the clinical laboratories at each of the centers in accordance with uniform procedures that were derived from American Thoracic Society guidelines. Reference equations of Crapo et al., were used for predicted values of pulmonary function ([16], [17], [18]).

To evaluate health-related quality of life (QOL), a generic measure, the Short Form-36 (SF-36), and two respiratory-specific measures, the St. George's Respiratory Questionnaire (SGRQ) and the UCSD Shortness of Breath Questionnaire (SOBQ), were obtained from all participants ([19], [20], [21]). For the SF-36, lower scores indicate poorer health with a normative score in the U.S. population of 50 ± 10 points ([21]). Alternatively, for the SGRQ and the SOBQ, higher scores indicate poorer respiratory-specific health, with a maximum score for the SGRQ of 100 points and for the SOBQ of 120 points ([19], [20]).

Statistical analysis

Baseline characteristics are presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Scatter plots and Pearson correlation coefficients were used to determine the association between lung function, QOL scores, and exercise measures. Correlation coefficients were compared using the method of Meng et al. ([22]). Univariate regression models were developed for 6MWD and maximum work with SGRQ and FEV_1in individual models. Multivariable linear regression models were then developed in a stepwise manner to estimate the magnitude and statistical confidence of the effect of FEV_1 and SGRQ Total Score on 6MWD and maximum exercise capacity, adjusting for age, gender, height, and weight. In order to use a similar metric for both 6MWD and maximum exercise capacity, both were analyzed as the percent of predicted value, calculated from literature values ([14], [15]). All statistics were performed using STATA software, version 8.2 (Stata Corporation; College Station, TX; 2004). P-values of less than 0.05 were considered statistically significant.

Results

Study population

The characteristics of the study population are listed in Table 1. A total of 1,217 participants had both 6MWT and maximum CPX; one participant did not complete the 6MWT. As defined by the study protocol, the population had severe airflow obstruction, hyperinflation, and a decreased carbon monoxide diffusing capacity (Dco). The study group was 95% Caucasian and 61% male. While there was a statistically significant correlation between 6MWD and CPX ($r = 0.57$, $p < 0.001$), there was considerable variability unaccounted for by the correlation (Figure 1A and Figure 1B and Figure 2).

Figure 1 The distribution of percent predicted maximum exercise capacity (Panel A) and percent predicted 6-minute walk distance (Panel B) are shown. The maximum exercise capacity is more skewed than the walking distance, and has a lower central tendency. There were two outliers for maximum exercise capacity that are not shown on the graph as the % predicted exercise capacity was greater than 150%.

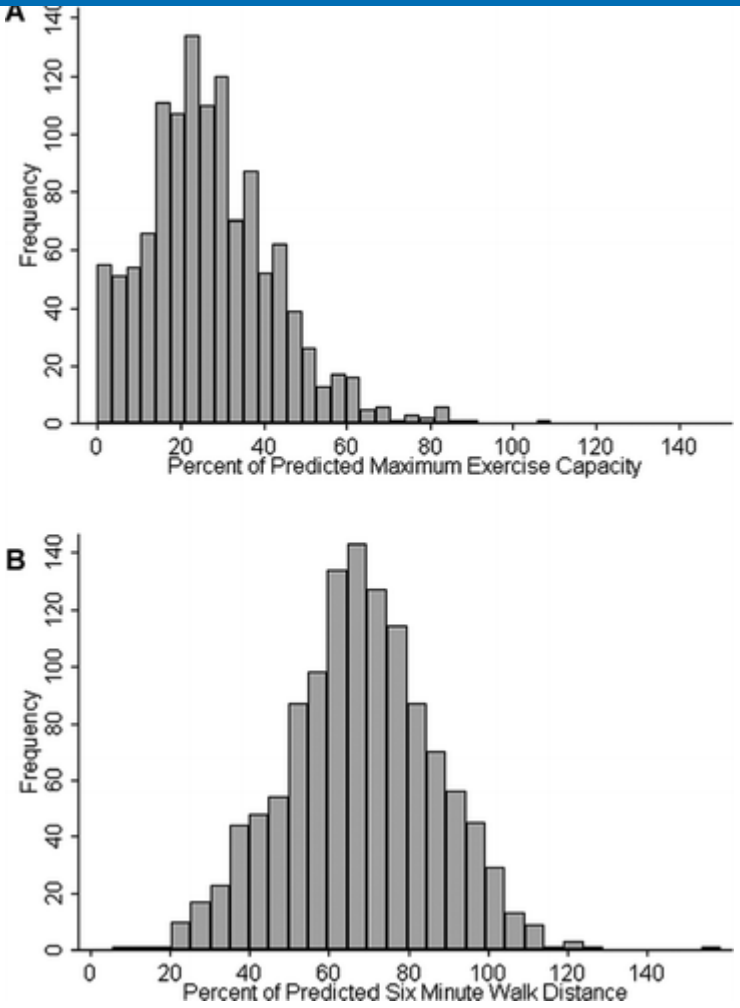

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Figure 2 Scatter plots of maximum exercise capacity (Watts) and 6-minute walk distance (feet) is shown with a best-fit polynomial regression line. The two tests are correlated with each other, but there is considerable variability.

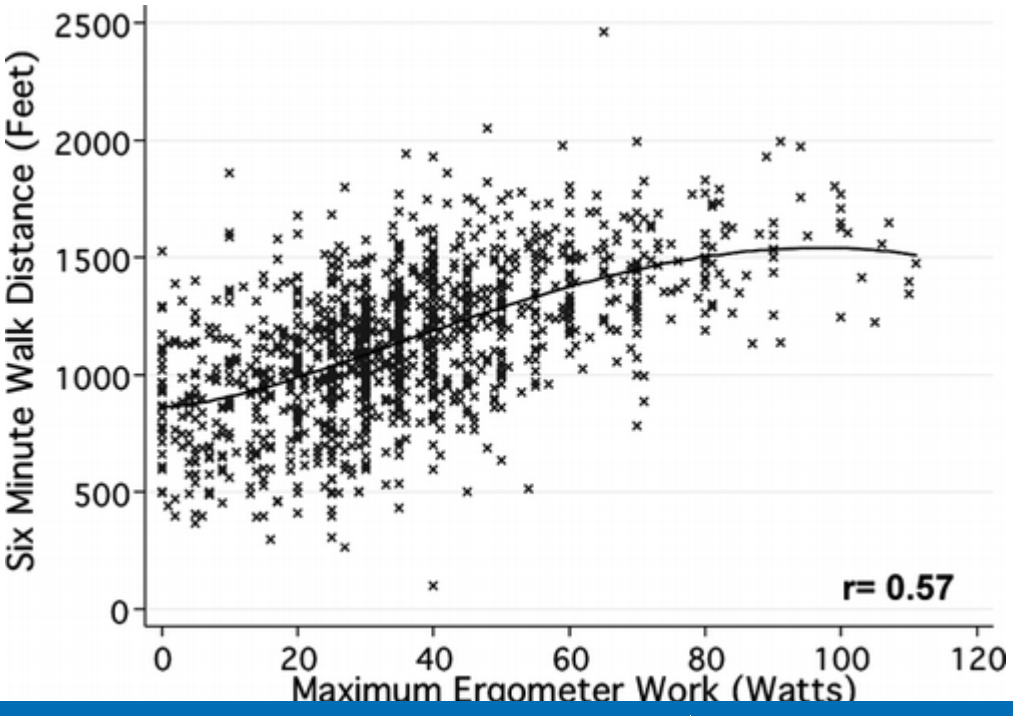

Table 1 Participant characteristics (N = 1218)

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Impairment in maximum exercise capacity was greater than the 6-minute walk distance compared to reference values (27.6 ± 16.8% predicted vs. 67.9 ± 18.9% predicted, $p < 0.001$). Moreover, the range of 6-minute walking distance was narrower and was more symmetrically distributed than maximum exercise capacity. The greater impairment in CPX compared to 6MWT is further illustrated by the fact that only 12 participants (1.0%) had a maximum exercise capacity greater than 80% predicted. In contrast, 308 (25.3%) of the study group had a 6-minute walk distance that was greater than 80% predicted. Alternatively, 34% of individuals had a maximum exercise capacity less than 20% predicted compared to only 2 (0.2%) of individuals who had a 6MWD less than 20% predicted. Additionally, 4.8% were unable to perform more than 5 watts of exercise compared to only 1.2% of the subjects who could walk no more than 500 feet, values that have previously been associated with poorer outcomes in COPD ([3], [23]).

The correlations between 6MWD, exercise capacity, and measures of pulmonary function are shown in Table 2 and Figure 3A and Figure 3B. The best correlates of exercise capacity were the FEV_1, IC, IC/TLC ratio and RV/TLC ratio. In general, maximum exercise capacity had a stronger correlation with measures of lung function than was the 6MWD ($p < 0.001$ for FEV_1 and IC). Additionally, IC had a similar correlation as FEV_1 with 6MWD ($r = 0.38$ vs. 0.38) and maximum ergometer work ($r = 0.59$ vs. 0.65). The partial correlations between FEV1 and maximum exercise capacity, adjusted for age gender, height, and weight were similar to the unadjusted values ($r = 0.53$ for maximum work, and $r = 0.37$ for 6MWD). The adjusted partial correlation between SGRQ and 6MWD ($r = -0.28$) was similar to the partial correlation between SGRQ and maximum work capacity ($r = 0.25$).

Figure 3 Scatter plots of FEV_1(liters) with six-minute walk distance (feet) (Panel A.) and maximum exercise capacity (Watts) (Panel B.) are shown. The FEV_1explains more of the variability of maximum exercise capacity ($r = 0.64$) than 6-minute walk distance ($r =$

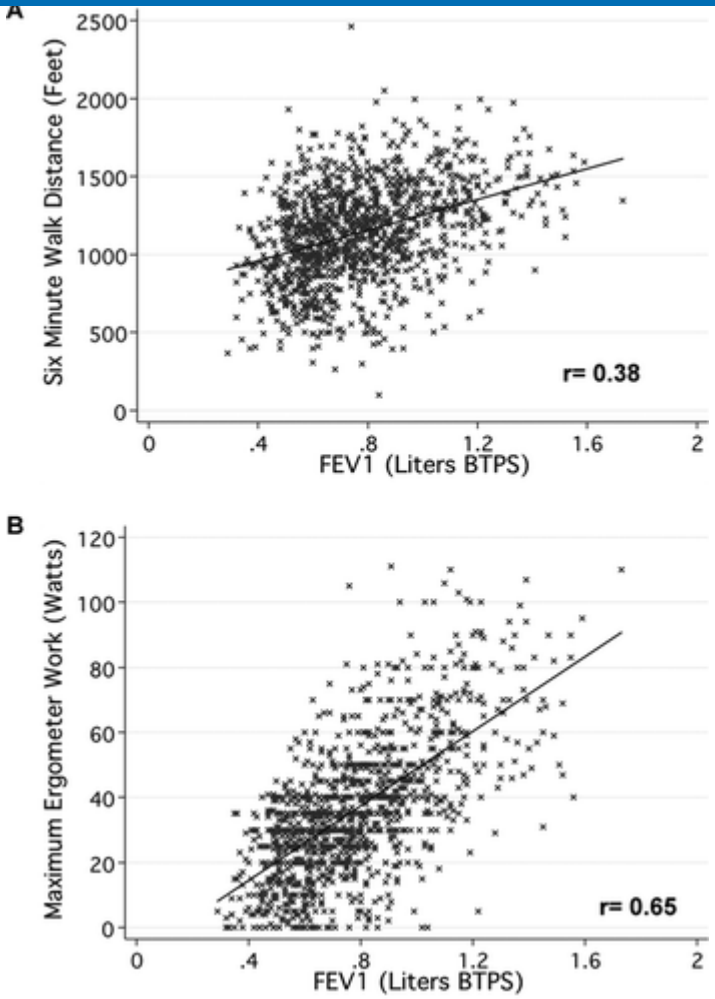

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Table 2 Pearson's Correlation Coefficients (r) between Exercise Tests, Lung Function and Quality of Life Measures

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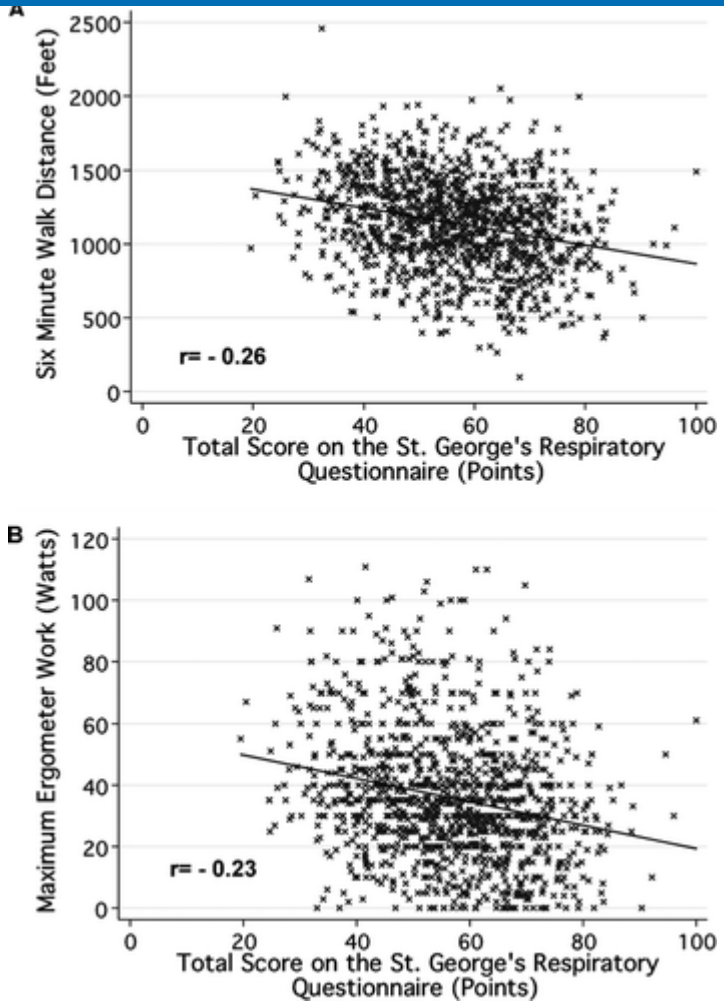
The correlations between 6MWD, maximum exercise capacity, and measures of quality of life are shown in Table 2 and Figure 4A and Figure 4B. The 6MWD was similarly correlated with measures of quality of life as maximum exercise performance. By univariate regression, the r^2 for the 6MWD explained only 6.8% of the variance in SGRQ while the r^2 for the CPX explained only 5.3% of this variance.

Figure 4 Scatter plots of SGRQ Total Score with 6-minute walk distance (feet) (Panel A) and maximum exercise capacity (Watts) (Panel B) are shown. The SGRQ explains slightly more of the variability of 6-minute walk ($r = -0.26$) than maximum exercise capacity ($r = -0.23$).



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In order to determine the relationships between the 6MWD and CPX with measures of lung function and quality of life, we constructed a linear regression model using percent of predicted 6MWD and maximum exercise capacity as outcome measures, and both FEV_1 and SGRQ total score as independent predictors (Table 3). Adjustment was made for age, gender, height and weight. The effect of lung function, as indicated by the FEV_1, was similar for both maximum exercise and 6-minute walk (31.8 ± 2.01 vs. 29.8 ± 2.39 increase in % predicted/L). After adjusting for pulmonary function, respiratory-specific quality of life, as indicated by the SGRQ, had a significantly smaller effect on maximum exercise capacity than on the six-minute walk (−0.25 ± 0.03 vs. −0.37 ± 0.04 change in % predicted/SGRQ unit). However, overall, more of the variability in maximum exercise was explained by FEV1 and SGRQ than for the six-minute walk (r^2 = 0.31 vs. 0.24.

Table 3 Regression Models for Exercise Measures

DISCUSSION

This study demonstrates that 6MWD and CPX, although significantly correlated, measure somewhat different domains of exercise performance in individuals with advanced emphysema. When results are expressed as percent of predicted, these individuals with severe emphysema have less impairment of the 6MWD than impairment of maximum exercise capacity. Indeed, despite a mean FEV_1 % predicted of 26.9%, participants achieved a mean of 68% predicted 6MWD and had remarkable preservation of their endurance given the degree of lung function impairment. Individuals with COPD, in general, exercise at a higher fraction of their maximum exercise capacity than normal individuals ([24]). Thus, we interpret these findings to indicate that individuals with severe lung function impairment can maintain walking distance through the use of submaximal ventilation that approaches but does not exceed their maximum sustainable ventilation. This is analogous to the relative preservation of submaximal exercise capacity relative to maximum exercise capacity that is seen in elderly individuals ([25]).

Performance on both exercise tests is correlated with ventilatory impairment indicated by standard lung function tests, particularly the $FEV_1$and IC. However, maximum exercise capacity is more closely correlated with lung function measures than six-minute walk distance. Presumably this reflects the close correlation of maximum exercise capacity with maximum ventilation in individuals with severe COPD ([26], [27], [28]). Our results suggest that maximum exercise capacity testing may underestimate the day-to-day submaximal functional capacity of individuals with severe COPD. On the other hand, maximum exercise testing provides a more accurate assessment of physiologic as well as maximal functional impairment.

Supplemental oxygen was used during both exercise tests to limit hypoxemia as a factor that might contribute to poor exercise performance. All participants received supplemental oxygen at an inspired oxygen concentration of 30% while performing the CPX. Similarly, patients who showed desaturation during treadmill exercise were given supplemental oxygen during the six-minute walk. Thus, the results from this study largely reflect exercise limitation due to mechanical ventilatory limitation rather than gas exchange limitation. Since hypoxemic patients were prescribed oxygen during

hypoxemia, we might have found better correlation of exercise capacity with diffusing capacity ([29]).

In univariate analysis, both the 6MWT and CPX were similarly correlated with quality of life measures as has been reported previously in the NETT population ([30]). Presumably, the impact of disease on daily activities is more closely related to the submaximal exercise of the 6MWT than by maximum exercise tests. Previously, the NETT investigators have reported that the SOBQ was slightly better in predicting both maximum exercise capacity and 6MWD than the SGRQ ([30]). However, both SOBQ and SGRQ were well correlated with each other ($r = 0.67$, $p < 0.0001$) suggesting that they measure similar features of the impact of respiratory disease. In contrast, the generic health-related QOL instrument, the SF-36 physical component summary, did not have a strong association with either exercise test.

Previous studies that have directly compared the measurement properties of the 6MWT and the CPX have shown variable results ([6]). There is a significant correlation between maximum oxygen consumption and 6MWD ($r = 0.51$) ([31]) and between maximum oxygen consumption and maximum work ($r = 0.58–0.81$) ([5], [32]). However, few studies have directly compared the results of the 6MWT and the CPX to their relationship with lung function and QOL measures. Wijkstra, et al, showed no significant difference in the correlation of lung function (FEV_1, RV, D_{CO}) with the CPX and 6MWT in forty individuals with severe COPD ($FEV_1 < 50\%$) ([32]). However, the 6MWD has been demonstrated to be more correlated with dyspnea as measured by the Borg Dyspnea Index in two previous small studies ([5], [32]).

The primary functional outcome measure for the NETT study was the maximum exercise capacity by bicycle ergometry ([13]). Insofar as this measure integrates both physiologic and quality of life measures, it is a meaningful primary outcome for a clinical trial in COPD. However, treatments such as pulmonary rehabilitation that improve endurance or promote coping strategies to improve submaximal exercise tolerance in the absence of changes in pulmonary physiology might have less impact on maximum exercise capacity than on the 6MWD. In contrast, treatments that improve lung function alone might have greater effect on maximum exercise capacity than on 6MWD. It should be noted, however, that patients with COPD may have very restricted daily exercise activity when measured by objective means ([33]).

One of the strengths of this study is that it represents a large group of individuals with lung disease well-characterized as emphysema. Because the study was done at 17 clinical centers, it is likely to be more generally representative than studies done at a single center. However, we are cautious about extending the results from this study to those with less severe COPD as the study population was limited to a narrow range of individuals with severe or very severe emphysema who were participating in a trial of lung volume reduction surgery. In addition, the CPX was performed while individuals were receiving 30% inspired oxygen, which is not a standard practice. Delivery of a fixed concentration of oxygen may not be feasible in many laboratories, and some individuals may have better maximum exercise performance while performing CPX on oxygen.

In conclusion, we have found that the 6MWT and CPX, although correlated with each other, measure different aspects of exercise capacity. The CPX better reflects aspects of both lung function and is more severely impaired by emphysema, whereas the 6MWT is more closely related to functional impairment in activities of daily life and is less impaired in severe emphysema.

ACKNOWLEDGMENTS

The members of the National Emphysema Treatment Trial Research Group were as follows: Office of the Chair of the Steering Committee, University of Pennsylvania, Philadelphia: A.P. Fishman, B.A. Bozzarello, A. Al-Amin. Clinical Centers: Baylor College of Medicine, Houston: M. Katz, C. Wheeler, E. Baker, P. Barnard, J. Carter, S. Chatziioannou, K. Conejo-Gonzales, J. Haddad, D. Hicks, N. Kleiman, M. Milburn-Barnes, C. Nguyen, M. Reardon, J. Reeves-Viets, S. Sax, A. Sharafkhaneh, C. Young, R. Espada, R. Butanda, K. Dubose, M. Ellisor, P. Fox, K. Hale, E. Hood, A. Jahn, S. Jhingran, K. King, C. Miller, I. Nizami, T. Officer, J. Ricketts, J. Rodarte, R. Teague, K. Williams; Brigham and Women's Hospital, Boston: J. Reilly, D. Sugarbaker, C. Fanning, S. Body, S. Duffy, V. Formanek, A. Fuhlbrigge, P. Hartigan, S. Hooper, A. Hunsaker, F. Jacobson, M. Moy, S. Peterson, R. Russell, D. Saunders, S. Swanson; Cedars–Sinai Medical Center, Los Angeles: R. McKenna, Z. Mohsenifar, C. Geaga, M. Biring, S. Clark, R. Frantz, P. Julien, M. Lewis, J. Minkoff-Rau, V. Yegyan, M. Joyner; Cleveland Clinic Foundation, Cleveland: M. DeCamp, J. Stoller, Y. Meli, J. Apostolakis, D. Atwell, J. Chapman, P. DeVilliers, R. Dweik,

Meziane, O. Minai, P. O'Donovan, M. Steiger, K. White, J. Maurer, C. Hearn, S. Lubell, R. Schilz, T. Durr; Columbia University, New York, and Long Island Jewish Medical Center, New Hyde Park, N.Y.: M. Ginsburg, B. Thomashow, P. Jellen, J. Austin, M. Bartels, Y. Berkman, P. Berkoski, F. Brogan, A. Chong, G. DeMercado, A. DiMango, B. Kachulis, A. Khan, B. Mets, M. O'Shea, G. Pearson, J. Pfeffer, L. Rossoff, S. Scharf, M. Shiau, P. Simonelli, K. Stavrolakes, D. Tsang, D. Vilotijevic, C. Yip, M. Mantinaos, M. McKeon; Duke University Medical Center, Durham, N.C.: N. MacIntyre, R.D. Davis, J. Howe, R.E. Coleman, R. Crouch, D. Greene, K. Grichnik, D. Harpole, A. Krichman, B. Lawlor, H. McAdams, J. Plankeel, S. Rinaldo-Gallo, J. Smith, M. Stafford-Smith, V. Tapson, M. Steele, J. Norten; Mayo Foundation, Rochester, Minn.: J. Utz, C. Deschamps, K. Mieras, M. Abel, M. Allen, D. Andrist, G. Aughenbaugh, S. Bendel, E. Edell, M. Edgar, B. Edwards, B. Elliot, J. Garrett, D. Gillespie, J. Gurney, B. Hammel, K. Hanson, L. Hanson, G. Harms, J. Hart, T. Hartman, R. Hyatt, E. Jensen, N. Jenson, S. Kalra, P. Karsell, D. Midthun, C. Mottram, S. Swensen, A.-M. Sykes, K. Taylor, N. Torres, R. Hubmayr, D. Miller, S. Bartling, K. Bradt; National Jewish Medical and Research Center, Denver: B. Make, M. Pomerantz, M. Gilmartin, J. Canterbury, M. Carlos, P. Dibbern, E. Fernandez, L. Geyman, C. Hudson, D. Lynch, J. Newell, R. Quaife, J. Propst, C. Raymond, J. Whalen-Price, K. Winner, M. Zamora, R. Cherniack; Ohio State University, Columbus: P. Diaz, P. Ross, T. Bees, H. Awad, J. Drake, C. Emery, M. Gerhardt, M. Kelsey, M. King, D. Rittinger, M. Rittinger; Saint Louis University, St. Louis: K. Naunheim, F. Alvarez, J. Osterloh, S. Borosh, W. Chamberlain, S. Frese, A. Hibbit, M.E. Kleinhenz, G. Ruppel, C. Stolar, J. Willey, C. Keller; Temple University, Philadelphia: G. Criner, S. Furukawa, A.M. Kuzma, R. Barnette, N. Brister, K. Carney, W. Chatila, F. Cordova, G. D'Alonzo, M. Keresztury, K. Kirsch, C. Kwak, K. Lautensack, M. Lorenzon, U. Martin, P. Rising, S. Schartel, J. Travaline, G. Vance, P. Boiselle, G. O'Brien; University of California, San Diego, San Diego: A. Ries, R. Kaplan, C. Ramirez, D. Frankville, P. Friedman, J. Harrell, J. Johnson, D. Kapelanski, D. Kupferberg, C. Larsen, T. Limberg, M. Magliocca, F.J. Papatheofanis, D. Sassi-Dambron, M. Weeks; University of Maryland at Baltimore, Baltimore, and Johns Hopkins Hospital, Baltimore: M. Krasna, H. Fessler, I. Moskowitz, T. Gilbert, J. Orens, S. Scharf, D. Shade, S. Siegelman, K. Silver, C. Weir, C. White; University of Michigan, Ann Arbor: F. Martinez, M. Iannettoni, C. Meldrum, W. Bria, K. Campbell, P. Christensen, K. Flaherty, S. Gay, P. Gill, P. Kazanjian, E. Kazerooni, V. Knieper, T. Ojo, L. Poole, L. Quint, P. Rysso, T. Sisson, M. True, B. Woodcock, L. Zaremba; University of Pennsylvania, Philadelphia: L. Kaiser, J. Hansen-Flaschen, M.L. Geraghty, A. Alavi, T. Alcorn, J. Aronchick, S. Aukberg, B. Benedict, S. Craemer, R. Daniele, J. Edelman, W. Gefter, J.

Sheaffer, R. Simcox, S. Snedeker, J. Stone-Wynne, G. Tino, P. Wahl, J. Walter, P. Ward, D. Zisman, J. Mendez, A. Wurster; University of Pittsburgh, Pittsburgh: F. Sciurba, J. Luketich, C. Witt, G. Ayres, M. Donahoe, C. Fuhrman, R. Hoffman, J. Lacomis, J. Sexton, W. Slivka, D. Strollo, E. Sullivan, T. Simon, C. Wrona, G. Bauldoff, M. Brown, E. George, R. Keenan, T. Kopp, L. Silfies; University of Washington, Seattle: J. Benditt, D. Wood, M. Snyder, K. Anable, N. Battaglia, L. Boitano, A. Bowdle, L. Chan, C. Chwalik, B. Culver, T. Gillespy, D. Godwin, J. Hoffman, A. Ibrahim, D. Lockhart, S. Marglin, K. Martay, P. McDowell, D. Oxorn, L. Roessler, M. Toshima, S. Golden.

Other participants included the following: Agency for Healthcare Research and Quality, Rockville, Md.: L. Bosco, Y.-P. Chiang, C. Clancy, H. Handelsman; Centers for Medicare and Medicaid Services, Baltimore: S. Sheingold, T. Carino, J. Chin, J. Farrell, K. McVearry, A. Norris, S. Shirey, C. Sikora; Coordinating Center, Johns Hopkins University, Baltimore: S. Piantadosi, J. Tonascia, P. Belt, K. Collins, B. Collison, J. Dodge, M. Donithan, V. Edmonds, J. Fuller, J. Harle, R. Jackson, H. Koppelman, S. Lee, C. Levine, H. Livingston, J. Meinert, J. Meyers, D. Nowakowski, K. Owens, S. Qi, M. Smith, B. Simon, P. Smith, A. Sternberg, M. Van Natta, L. Wilson, R. Wise; Cost-Effectiveness Subcommittee: R.M. Kaplan, J.S. Schwartz, Y-P. Chiang, M.C. Fahs, A.M. Fendrick, A.J. Moskowitz, D. Pathak, S. Ramsey, S. Sheingold, A.L. Shroyer, J. Wagner, R. Yusen; Cost-Effectiveness Data Center, Fred Hutchinson Cancer Research Center, Seattle: S. Ramsey, R. Etzioni, S. Sullivan, D. Wood, T. Schroeder, R. Smith, K. Berry, N. Myers; CT Scan Image Storage and Analysis Center, University of Iowa, Iowa City: E. Hoffman, J. Cook-Granroth, A. Delsing, J. Guo, G. McLennan, B. Mullan, C. Piker, J. Reinhardt, J. Sieren, W. Stanford; Data and Safety Monitoring Board: J.A. Waldhausen, G. Bernard, D. DeMets, M. Ferguson, E. Hoover, R. Levine, D. Mahler, A.J. McSweeny, J. Wiener-Kronish, O.D. Williams, M. Younes; Marketing Center, Temple University, Philadelphia: G. Criner, C. Soltoff; Project Office, National Heart, Lung, and Blood Institute, Bethesda, Md.: G. Weinmann, J. Deshler, D. Follmann, J. Kiley, M. Wu.

Other acknowledgements: Arthur Gelb, MD, Lakewood Regional Medical Center, Lakewood, CA

Funding: Supported by contracts with the National Heart, Lung, and Blood Institute (N01HR76101, N01HR76102, N01HR76103, N01HR76104, N01HR76105, N01HR76106, N01HR76107, N01HR76108, N01HR76109, N01HR76110, N01HR76111, N01HR76112, N01HR76113, N01HR76114, N01HR76115, N01HR76116, N01HR76118, and

N01HR76119), the Centers for Medicare and Medicaid Services, and the Agency for Healthcare Research and Quality

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