A new maximal bicycle test using a prediction algorithm developed from four large COPD studies

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ABSTRACT

Background: Maximum exercise workload (W_{MAX}) is today assessed as the first part of Cardiopulmonary Exercise testing. The W_{MAX} test exposes patients with COPD, often having cardiovascular comorbidity, to risks. Our research project was initiated with the final aim to eliminate the W_{MAX} test and replace this test with a predicted value of W_{MAX} based on a prediction algorithm of W_{MAX} derived from multicentre studies.

Methods: Baseline data (W_{MAX}, demography, lung function parameters) from 850 COPD patients from four multicentre studies were collected and standardized. A prediction algorithm was prepared using Random Forest modelling. Predicted values of W_{MAX} were used in a new W_{MAX} test, which used a linear increase in order to reach the predicted W_{MAX} within 8 min. The new W_{MAX} test was compared with the standard stepwise W_{MAX} test in a pilot study including 15 patients with mild/moderate COPD.

Results: The best prediction algorithm of W_{MAX} included age, sex, height, weight, and six lung function parameters. FEV1 and DLCO were the most important predictors. The new W_{MAX} test had a better correlation (R^2 = 0.84) between predicted and measured W_{MAX} than the standard W_{MAX} test (R^2 = 0.66), with slopes of 0.50 and 0.46, respectively. The results from the new W_{MAX} test and the standard W_{MAX} test correlated well.

Conclusion: A prediction algorithm based on data from four large multicentre studies was used in a new W_{MAX} test. The prediction algorithm provided reliable values of predicted W_{MAX}. In comparison with the standard W_{MAX} test, the new W_{MAX} test provided similar overall results.

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Introduction

Spirometry is mandatory for establishing a diagnosis of chronic obstructive pulmonary disease (COPD) but is not sufficient for a general clinical assessment and evaluation of potential treatment effects. Functional performance assessed at walk or bicycle exercise tests together with measurements of symptoms and health-related Quality of Life (QoL) provide valuable additional information about present disease status, as well as prediction of future risk of exacerbations and disease prognosis [1–7]. The standard bicycle exercise protocol for cardiopulmonary exercise testing (CPET) measures the endurance time of cycling during a standard endurance test, at a constant rate of 75% of the maximum exercise workload (W_{MAX}) [7–11]. W_{MAX} is obtained in a preceding incremental W_{MAX} test, in which the patient is subjected to a stepwise increase in workload until the point of physical exhaustion or another symptom-limited reason for stopping is reached.

CPET is technically demanding and requires expensive equipment [11]. A considerable number of participants are needed to detect potential therapeutic effect differences due to high inter- and intra-test variability of the standard endurance test [8,10,12,13]. In addition, CPET is associated with a certain increase in cardiac risks, particularly at the initial W_{MAX} test [7,8].

A way to address the above downsides would be to correctly predict W_{MAX}, which optimally could avoid the W_{MAX} test by using 75% of the predicted value for the endurance test. Several papers have identified predictors for W_{MAX} or maximal oxygen consumption (VO2_{MAX}) in COPD patients using the standard W_{MAX} or VO2_{MAX} test. Forced expiratory volume in 1 sec (FEV1) has been identified as an important predictor [14–19]. Other predictors identified are static lung volumes (e.g. inspiratory capacity; IC) [14,15,18],

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small airway dysfunction, e.g. reduced mid-expiratory flow (FEF<sub>25-75</sub>) [17,20,21], impaired gas exchange measured by e.g. diffusing capacity for carbon monoxide (DLCO) [14,15,18,20,22], maximal voluntary ventilation (MVV) [18,19,21], Medical Research Council (MRC) scale [16,17], sub-maximal exercise [23,24] and demographic data such as sex, age, body-mass index (BMI) or fat-free mass [14–17,20,21,25]. However, another article concluded that predicted VO<sub>2</sub>MAX from baseline characteristics cannot be used for patients with stable COPD [26].

Previous papers claiming predictability of W<sub>MAX</sub> (VO<sub>2</sub>MAX) had different reasons for trying to replace the incremental test by a predictive (W<sub>MAX</sub> or VO<sub>2</sub>MAX) value, e.g. to determine an individual patient’s future risks of, e.g., exacerbations, to avoid complication in a cardiopulmonary risk population, to reduce costs caused by expensive equipment and to achieve a reasonably accurate endurance value for a rehabilitation program. Only one study [27] has specifically addressed the possibility to predict the individual incremental step increase to keep the test to 8–10 min (see also [16,28]). Most previous prediction papers have used stepwise and not linear increase. A number of older studies concluded that a linear ramp test was no better than a stepwise incremental test (for an overview, see [8]), but these papers could be challenged.

We, therefore, embarked on a research project aiming to improve CPET by

1. elimination of the incremental W<sub>MAX</sub> test in order to avoid the cardiovascular risks associated with the test and, in addition, save clinical study resources. Instead, a carefully predicted value of W<sub>MAX</sub> is to be used to identify the starting point for the 75% endurance test.
2. decreasing the usually high intra- and inter-ramping variability of the 75% endurance test and thereby offer comparative COPD study designs needing less patients.

As an initial step, we designed a new model for the incremental W<sub>MAX</sub> test involving three combined ideas to be tested: 1) a prediction algorithm, developed from four large pharmaceutical industry-sponsored clinical studies, in order to identify a predicted value of W<sub>MAX</sub> to be reached within a certain exercise time (3 + 8 min; see Figure 1); 2) a linear instead of stepwise increase of workload to introduce continuous W<sub>MAX</sub> values instead of categorical values of 10 W per step. 3) measurements of future predictors (e.g. low-intensity O<sub>2</sub>/CO<sub>2</sub> kinetic evaluation, impulse oscillometry and activity scores).

The proposed new W<sub>MAX</sub> test was compared with the standard incremental W<sub>MAX</sub> test [8] in a single-centre pilot study. This report includes two major parts – the development of the prediction algorithm and the results from the pilot study.

The primary objective of the pilot study was to verify the prediction algorithm using the new W<sub>MAX</sub> test. The secondary objective was to show that the new W<sub>MAX</sub> test provided better results compared to the standard W<sub>MAX</sub> test, for use in future studies within this research project. This new W<sub>MAX</sub> test will be utilized until the prediction model provides values of W<sub>MAX</sub> that are reliable enough to be used as the starting point for the 75% endurance test.

Materials and methods

Studies used for developing a prediction algorithm of W<sub>MAX</sub>

Patients

Baseline data (demography, lung function parameters and W<sub>MAX</sub> from incremental exercise tests) were provided from two pharmaceutical companies (AstraZeneca and Boehringer Ingelheim) via standard data-sharing agreements. Patients with COPD participated in four multicentre, randomised clinical studies examining the effects of tiotropium (Study A,B,D) [12,13,29] or budesonide/
formoterol (Study C) [30] on exercise performance (Table 1). The inclusion criteria were similar in Study A-C, while Study D included patients with milder COPD. Patients were clinically stable patients with COPD, aged >40 years, with a smoking history of >10 pack-years, a pre-bronchodilator FEV1 ≤ 65% (Study A and B) or of predicted normal, ≤50% (Study C) or 50–80% (Study D). Studies were approved by medical ethical committees and all patients gave written informed consent before undertaking any study procedures.

**Study design**

In Study A-D eligibility criteria were assessed during an initial screening visit. At this or a following pre-randomization visit, patients performed pulmonary function tests followed by a standard incremental WMAX test. Study A-C were conducted using bicycle exercise testing while Study D used treadmill exercise testing.

The data were combined into a single dataset following transformations in order to account for differences in units, data formats and naming of the variables. Note that all variables were not available from all studies.

**Outcome measures**

For the post hoc analysis of Study A-D, the outcome was a prediction algorithm for the best possible prediction of WMAX.

**Statistical analyses**

Prediction algorithms were formulated using Random Forest modelling [31] for each of Study A-D separately. The Random Forest model was used to automatically handle potential non-linear associations among the variables (predictors). A list of the ranking order among the variables was obtained, sorted in descending order with the best predicting variable first. Random Forest modelling was performed using R (v 3.5.1 for Mac) software. Univariate regression was performed in Microsoft Excel for Office 365. The Random Forest algorithms are available for external use upon request.

**Pilot study to compare new and standard WMAX test**

**Patients**

In the pilot study, patients with COPD who had no exacerbations of COPD within the last 6 weeks, a post-bronchodilator FEV1 of ≥40 to ≤80% of predicted normal and no cardiovascular co-morbidity preventing exercise testing were included. The Regional Ethical Review Board approved the study. Written informed consent was obtained from all patients prior to any study procedures. Patients were out-patients who had previously visited our clinic and registered for volunteering in other research studies.

**Table 1.** Patient baseline characteristics per study for study A-D and the pilot study.

| Study code | Study A | Study B | Study C | Study D |
|------------|---------|---------|---------|---------|
| Sponsor    | BI      | BI      | AZ      | BI      |
| Reference  | [13]    | [12]    | [30]    | [29]    |
| ClinicalTrials.gov identifier | NCT00274508 | NCT00530842 | NCT00489853 | NCT01072396 |

Number of patients
Age, years
Male, %
Height, cm
Weight, kg
BMI, kg/m²
Caucasian, % (race)
Afro-American, % (race)
Current smoker, %
Pack years
COPD duration, years
LABA user, %
ICS user, %
LAMA user, %
FEV1, L **
FEV1, % predicted ***
FVC, L **
FEV1/FVC % **

Values are mean ± standard deviation unless otherwise specified.
AZ, AstraZeneca; BMI, Body-mass index; BI, Boehringer Ingelheim; FEV1, forced expiratory volume in 1 sec; FVC, Forced vital capacity; ICS, Inhaled corticosteroid; LABA, Long-acting β2 adrenoceptor agonist; LAMA, Long-acting muscarinic receptor antagonist.

* 80% had COPD duration >5 years; 20% had COPD duration 2–5 years
** Pre-bronchodilator (Study A-D); post-bronchodilator (Pilot study).
*** % of predicted normal, calculated according to NHANES III.
Study design
The study was non-blinded and single-centre. At visit 1, demography data, modified medical research council (MMRC) dyspnea scale scores and clinical COPD questionnaire (CCQ) scores were collected. The COPD patients performed lung function tests (spirometry, body plethysmography, CO-diffusion test and impulse oscillometry) after inhalation of 400 µg salbutamol. The predicted value of $W_{\text{MAX}}$ for each patient was calculated on a pre-programmed computer holding the Random Forest algorithm.

Patients then performed the standard or the new $W_{\text{MAX}}$ test in a random cross-over fashion at the following visits. During the standard test, after a few minutes of sitting on the bicycle in order to stabilize the oxygen kinetics measurement equipment, the patient had an approximately one-minute warm-up period of loadless pedalling, followed by an incremental increase in workload with 10 W per minute until the patient reached his/her $W_{\text{MAX}}$ at the point of exhaustion. During the new $W_{\text{MAX}}$ test, the patients started cycling at a load of 40% of the predicted $W_{\text{MAX}}$ for 3 min, followed by a linear increase in load, calculated to reach the predicted $W_{\text{MAX}}$ after an additional 8 min (Figure 1). In both $W_{\text{MAX}}$ tests, the same safety procedure were applied, as recommended for the standard $W_{\text{MAX}}$ test [7,8]. Borg scale results were collected at every 2 min during both tests [32].

Outcome measures
The primary outcome measure was the ability of the prediction algorithm to successfully predict $W_{\text{MAX}}$ as shown by the coefficient of determination ($R^2$) between predicted and measured $W_{\text{MAX}}$ at the new $W_{\text{MAX}}$ test. Secondary outcome variables were descriptive comparisons between the new and the standard $W_{\text{MAX}}$ test for averages of measured $W_{\text{MAX}}$ and work performed, reasons for stopping exercise and Borg scale results.

Statistical analyses
We designed the study to include 15–20 patients in order to obtain enough data to test the prediction model and to compare the new test with the standard test, but no formal power calculation was performed. The comparisons between predicted and measured $W_{\text{MAX}}$ and the new and the standard $W_{\text{MAX}}$ test were performed using univariate regression, descriptive statistics and Bland–Altman graphs [33]. Microsoft Excel for Office 365 was used for univariate regression analyses and Bland–Altman graphs. Demographics and patient data were expressed as mean ± standard deviation.

Results
Studies used for developing a prediction algorithm of $W_{\text{MAX}}$
In total, 850 patients with COPD were included in the dataset for Study A-D, and their baseline data are summarized in Table 1. Using Random Forest modelling, all lung function and demographic variables for each of Study A-D were assessed for their ability to predict $W_{\text{MAX}}$. Results are presented in Table 2. The best percentage of variance explained was obtained for Study A, followed by Study B, C and D. The six best

Table 2. Rank order for prediction ability for different variables from Random Forest modelling in study A-D.

| Study A | Rank | Variable  | Study B | Rank | Variable | Study C | Rank | Variable | Study D | Rank | Variable |
|---------|------|-----------|---------|------|----------|---------|------|----------|---------|------|----------|
| 1       | 1    | FEV₁      | 1       | 1    | FEV₁     | 1       | 1    | FEV₁     | 1       | 1    | FEV₁     |
| 2       | 2    | DLCO      | 2       | 2    | FVC      | 2       | 2    | IC       | 2       | 2    | IC       |
| 3       | 3    | FEF₅₀     | 3       | 3    | BODY₉₂_VC| 3       | 3    | FVC      | 3       | 3    | FVC      |
| 4       | 4    | VA        | 4       | 4    | IC       | 4       | 4    | DLCO     | 4       | 4    | DLCO     |
| 5       | 5    | FVC       | 5       | 5    | RV       | 5       | 5    | SVC      | 5       | 5    | SVC      |
| 6       | 6    | FEF₂₅₋₇₅ | 6       | 6    | FRC      | 6       | 6    | Height   | 6       | 6    | Height   |
| 7       | 7    | TLC       | 7       | 7    | Weight   | 7       | 7    | RV       | 7       | 7    | RV       |
| 8       | 8    | FEF       | 8       | 8    | SPIR₂₀_VC| 8       | 8    | Weight   | 8       | 8    | Weight   |
| 9       | 9    | SVC       | 9       | 9    | TLC      | 9       | 9    | TGV      | 9       | 9    | TGV      |
| 10      | 10   | RV        | 10      | 10   | Height   | 10      | 10   | FRC      | 10      | 10   | FRC      |
| 11      | 11   | Height    | 11      | 11   | Age      | 11      | 11   | AGE      | 11      | 11   | RAW      |
| 12      | 12   | Weight    | 12      | 12   | Weight   | 12      | 12   | Weight   | 12      | 12   | Weight   |
| 13      | 13   | Age       | 13      | 13   | Age      | 13      | 13   | Age      | 13      | 13   | Age      |
| 14      | 14   | TGV       | 14      | 14   | TGV      | 14      | 14   | TGV      | 14      | 14   | TGV      |
| 15      | 15   | RAW       | 15      | 15   | RAW      | 15      | 15   | RAW      | 15      | 15   | RAW      |
| 16      | 16   | SGAW      | 16      | 16   | SGAW     | 16      | 16   | SGAW     | 16      | 16   | SGAW     |
| Nd      | Nd   | FRC       | Nd      | Nd   | FRC      | Nd      | Nd   | FRC      | Nd      | Nd   | FRC      |

DLCO, diffusing capacity for carbon monoxide; FEF, forced expiratory flow; FEF₂₅₋₇₅, mid-expiratory flow; FEF₅₀, forced expiratory volume in 1 sec; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; Nd, not determined; RAW, airway resistance; RV, residual volume; SGAW, specific airway conductance; SVC, slow vital capacity; TGV, thoracic gas volume; TLC, total lung capacity; VA, alveolar volume; VC, vital capacity.
lung function variables in Study A were FEV\textsubscript{1}, DLCO, forced expiratory flow at 50% (FEF\textsubscript{50}), forced vital capacity (FVC), alveolar volume (VA) and FEF\textsubscript{25-75}.

Random Forest modelling for Study B-D (Table 2) showed that FEV\textsubscript{1} was the highest ranked variable in all three studies. In patients with the most severe COPD disease (Study C), predictors after FEV\textsubscript{1} were FVC, vital capacity (VC), IC and residual volume (RV). In Study D (the study with subjects with milder COPD disease), FEV\textsubscript{1} was followed by IC, FVC and DLCO. In Study B, FEV\textsubscript{1}, FVC and VC dominated as predictors. Neither Study B nor Study C included measurements of DLCO. Absolute values showed better results than % of predicted values. Univariate regression analyses of measured W\textsubscript{MAX} versus individual values for each variable are presented in Table 3.

Table 3 shows that DLCO, together with FEV\textsubscript{1}, was the best predictor in Study A. It was decided to base the prediction algorithm on the results from this study only, since the other study with measurements of DLCO (Study D) was a study using treadmill walking in patients with mild COPD. The lung function variables listed above from Study A were selected for the prediction algorithm, together with age, sex, height and weight. The results from the prediction algorithm are presented in the Figure 2, where predicted W\textsubscript{MAX} has been plotted versus measured W\textsubscript{MAX} for Study A. An R\textsuperscript{2}-value of 0.95 and a slope of 0.77 was observed.

![Figure 2. Predicted W\textsubscript{MAX} versus measured W\textsubscript{MAX} for Study A from the Random Forest prediction algorithm. Line is the line of identity.](image-url)

**Pilot study to compare new and standard W\textsubscript{MAX} test**

**Patient population**

A total of 19 patients were enrolled between July and October 2015. Fifteen of these were included in the study. Three were excluded due to FEV\textsubscript{1} ≥ 80% pre-

| Table 3. Results from univariate regression analyses of individual values from each parameter versus measured W\textsubscript{MAX} in study A-D and the pilot study. |
|-----------------|---------------|---------------|---------------|---------------|----------------|---------------|
| Variable*       | Study A       | Study B       | Study C       | Study D       | Pilot study, standard test** | Pilot study, new test*** |
|                 | R\textsuperscript{2} | R\textsuperscript{2} | R\textsuperscript{2} | R\textsuperscript{2} | R\textsuperscript{2} | R\textsuperscript{2} |
| FEV\textsubscript{1} | 0.41          | 0.32          | 0.30          | 0.28          | 0.44            | 0.67           |
| DLCO            | 0.37          | nd            | nd            | 0.21          | 0.78            | 0.75           |
| VA              | 0.26          | nd            | nd            | nd            | 0.10            | 0.23           |
| FEF\textsubscript{50} | 0.25         | nd            | nd            | nd            | 0.43            | 0.49           |
| FVC             | 0.20          | 0.22          | 0.24          | 0.26          | 0.06            | 0.20           |
| SVC             | 0.16          | 0.20          | 0.27          | 0.26          | 0.04            | 0.17           |
| FEF\textsubscript{25-75} | 0.15         | nd            | nd            | nd            | 0.53            | 0.63           |
| Weight          | 0.14          | 0.16          | 0.23          | 0.11          | 0.25            | 0.32           |
| Height          | 0.13          | 0.21          | 0.12          | 0.21          | 0.29            | 0.29           |
| Age             | 0.07          | 0.07          | 0.02          | 0.05          | 0.16            | 0.15           |
| TLC             | 0.03          | 0.0005        | nd            | 0.13          | 0.02            | 0.05           |
| RAW             | 0.03          | nd            | nd            | 0.05          | nd              | nd             |
| SGAW            | 0.03          | nd            | nd            | nd            | nd              | nd             |
| TGV             | 0.004         | 0.002         | nd            | 0.006         | 0.03            | 0.05           |
| RV              | 0.002         | nd            | 0.10          | 0.008         | 0.004           | 0.02           |
| IC              | nd            | nd            | 0.23          | 0.31          | 0.29            | 0.36           |
| FRC             | nd            | nd            | 0.06          | 0.002         | nd              | nd             |
| VC              | nd            | nd            | 0.23          | nd            | 0.04            | 0.17           |

*Sorted by rank order no in Study A

** Value vs measured W\textsubscript{MAX} in standard maximum test

*** Value vs measured W\textsubscript{MAX} in new maximum test

DLCO, diffusing capacity for carbon monoxide; FEF\textsubscript{25-75}, mid-expiratory flow; FEF\textsubscript{50}, forced expiratory flow ~ 50%; FEV\textsubscript{1}, forced expiratory volume in 1 sec; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; Nd, not determined; RAW, airway resistance; RV, residual volume; SGAW, specific airway conductance; SVC, slow vital capacity; TGV, thoracic gas volume; TLC, total lung capacity; VA, alveolar volume; VC, vital capacity.
dicted and one due to significant cardiovascular co-
morbidity. Fifteen patients with COPD were included
in the pilot study. They had a mean age of 71 years and
mean FEV\textsubscript{1} was 60% predicted normal. Further patient
baseline characteristics are presented in Table 1.

**Ability of the prediction algorithm to predict W\textsubscript{MAX}**

Figure 3 shows the correlation of predicted W\textsubscript{MAX} versus measured W\textsubscript{MAX} for the two tests (Figure 3(a,b)) plus the corresponding Bland–Altman plots (Figure 3(c,d)). Predicted values of W\textsubscript{MAX} correlated well with measured W\textsubscript{MAX} for the new test ($R^2 = 0.84$). For the standard test, a smaller determination coefficient was observed ($R^2 = 0.66$), even though the prediction algorithm was based on the standard W\textsubscript{MAX} test performed in Study A. The slope for predicted W\textsubscript{MAX} versus measured W\textsubscript{MAX} was 0.50 for the new test and 0.46 for the standard test.

**Comparison of the standard and new W\textsubscript{MAX} test**

The prediction algorithm from Study A was used for the new W\textsubscript{MAX} test. Similar average results were obtained for W\textsubscript{MAX}, work capacity, time of exercise, Borg scale results and reasons for stopping exercise at the two tests (Table 4). For W\textsubscript{MAX} reached (Figure 4, part A) and work performed in kWs (Figure 4, part B), $R^2$-values of 0.90 (W\textsubscript{MAX}) and 0.95 (work capacity) were observed when the standard test and the new test were compared. A higher amount of work with a lesser percentage deviation was achieved during the new W\textsubscript{MAX} test (47.5 kWs ± 36% SD) than during the standard W\textsubscript{MAX} test (35.5 kWs ±45% SD) (Table 4). The average duration was 9.3 ± 2.6 min (excluding the initial 3 min at 40% of predicted W\textsubscript{MAX}) for the new test compared to 10.6 ± 2.6 min for the standard test.

**Significance of DLCO**

DLCO was the variable with the highest $R^2$-value from univariate regression (0.78; Table 3) in the pilot study, which demonstrates its high ability for prediction of W\textsubscript{MAX} in a small single-centre study. In Study A (a multi-centre study), univariate regression gives a mean $R^2$-value of 0.37 for DLCO, but with a large inter-centre variability (range from 0.01 to 0.83 for the individual centres; data not shown).

![Figure 3](image-url) Predicted W\textsubscript{MAX} versus measured W\textsubscript{MAX} (a and b) and Bland–Altman plots (c and d) for the standard (a and c) and new (b and d) maximum test from the pilot study using the Random Forest algorithm. Line in A and B is the line of identity.
Discussion

In our search for a prediction algorithm with the ability to accurately predict $W_{\text{MAX}}$ to a level where standard incremental $W_{\text{MAX}}$ test can be eliminated, we investigated baseline lung function and demographic data together with results from a standard incremental $W_{\text{MAX}}$ test from four large pharmaceutical industry-sponsored clinical studies. Since DLCO was found to have outstanding abilities for prediction of $W_{\text{MAX}}$, a prediction algorithm was built using Random Forest modelling of data from only one of these four studies, a multicentre study with 261 patients. FEV$_1$ was another an excellent predictor, as was also observed in the three remaining studies, but these studies either lacked measurements of DLCO or used treadmill rather than bicycle exercise testing. The obtained prediction algorithm was utilized to set the low-intensity start and the linear increase in the new linear $W_{\text{MAX}}$ test in a pilot study. This study compared the new $W_{\text{MAX}}$ test with the standard incremental $W_{\text{MAX}}$ test. The prediction algorithm was successful in providing reliable values of predicted $W_{\text{MAX}}$, and the measured value of $W_{\text{MAX}}$ from the new test correlated better with the predicted value than did the corresponding value from the standard test. The $R^2$-value (our primary variable) was 0.84 for predicted vs measured $W_{\text{MAX}}$ for the new test. It should, however, be noted that the new $W_{\text{MAX}}$ test will possess the same cardiovascular risks as the standard $W_{\text{MAX}}$ test.

In comparison with the standard $W_{\text{MAX}}$ test, the new $W_{\text{MAX}}$ test provided similar overall results for work capacity, time of exercise, Borg scale results and reasons for stopping exercise. The slope for predicted $W_{\text{MAX}}$ versus measured $W_{\text{MAX}}$ was 0.50 (new test) and 0.46 (standard test), respectively, indicating that, for both tests, $W_{\text{MAX}}$ in the high range obtained from high performers are underestimated by the prediction algorithm and that $W_{\text{MAX}}$ in the low range (low performers) are overestimated by the prediction algorithm. The conformity was best for patients with mid-range $W_{\text{MAX}}$ values and hence the prediction algorithm needs further improvement. An improved prediction algorithm would improve the precision of the new $W_{\text{MAX}}$ test, so that the endurance test will be performed at an optimal level. If the patient starts the endurance test at too low or too high values as derived from the $W_{\text{MAX}}$ test, too long or too short endurance times may be observed leading to an increased intra-test variability.

The two tests correlated well with measured $W_{\text{MAX}}$, but the new linear test gave continuous data (not 10W stepwise data) along the regression line and achieved the predicted value of $W_{\text{MAX}}$ in $9.3 \pm 2.4$ min (programmed value 8 min), which meant that the increase was adapted to the respective individual. This resulted in a higher amount of performed work with less deviation. The

Table 4. Results of the standard maximum test and new maximum test performed in the pilot study.

|                      | Standard maximum test | New maximum test |
|----------------------|-----------------------|------------------|
| $W_{\text{MAX}}$ (W) | 107 ± 22              | 105 ± 23         |
| Time of exercise (min) | 10.6 ± 2.4             | 9.3 ± 2.4*       |
| Work performed (kWs) | 35.5 ± 16              | 47.5 ± 17**      |
| Borg dyspnea score, peak | 8.5 ± 2.0             | 8.7 ± 1.4        |
| Borg leg discomfort score, peak | 17.5 ± 1.8   | 17.6 ± 1.9      |
| Reason for stopping exercise, n (%)*** |                      |                  |
| Dyspnea               | 7 (47)                 | 8 (53)           |
| Dyspnea plus leg discomfort | 5 (33)             | 6 (40)          |
| Leg discomfort        | 3 (20)                 | 1 (7)            |

Values are mean ± standard deviation unless otherwise specified.
* Excluding the initial 3 min bicycling at 40% of predicted $W_{\text{MAX}}$
** Including the initial 3 min bicycling at 40% of predicted $W_{\text{MAX}}$
*** Reported as dyspnea, leg discomfort, both of these or other reasons

$y = 0.99x - 0.78; R^2 = 0.90$
$y = 1.06x + 9.99; R^2 = 0.94$

Figure 4. Measured $W_{\text{MAX}}$ (A) from and measured work performed (B) during the new maximum test versus the standard maximum test. Line is the line of identity.

Table 4. Results of the standard maximum test and new maximum test performed in the pilot study.
standard test and the new test showed similar mean \( W_{\text{MAX}} \), but the amount of work performed in kWs was constantly higher for the new method for both low and high performers. This is partly explained by the initial 3 min of bicycling at 40% of \( W_{\text{MAX}} \), but this accounts only for some 30–40% of the difference. The rest of the difference may be explained by the individualized increase in work overtime. In the standard test the load started at 10 W (but can be 30–40 W based on the experience of the investigator). The incremental steps were 10 W (but steps from 5 to 20 W have been utilized), and higher increases than 10 W have been pointed out to be beneficial [8]. In the new test, the initial low load and the following linear increase to \( W_{\text{MAX}} \) are personalized. The bicycle is programmed to reach the predicted \( W_{\text{MAX}} \) in 8 min; i.e. a predicted high performer faces a much steeper increase than a predicted low performer. Also, the precision of \( W_{\text{MAX}} \) is lower in the standard test, since work performed is calculated based on 10W-increments. This is exemplified in Figure 3 where five patients have a measured \( W_{\text{MAX}} \) of 100 W in the standard test.

A large number of prediction formulas for \( W_{\text{MAX}} \) or \( V_{\text{O2MAX}} \) in COPD patients have been presented [14–25,27,28]. Most of these have been derived from single-centre studies with low numbers of patients, and the generalizability of these formulas to broader COPD populations and to multicentre studies can be questioned. We took another approach by using data from large multicentre studies sponsored by pharmaceutical companies. The resulting prediction algorithm might be more accurate and generalizable as compared to most previous prediction equations of \( W_{\text{MAX}} \) due to the bigger and broader COPD populations included in the analyses. However, the multicentre data includes many centres with different qualities in performing a correct \( W_{\text{MAX}} \) test. For DLCO, problems with standardisation across centres and large coefficients of variation have been observed [34]. A good and generalizable prediction algorithm could be helpful to achieve the best possible measured \( W_{\text{MAX}} \) in order to have the 75% level in the endurance test as accurate as possible.

One of our major learnings is that the single and multicentre approach identified very similar predictors. Our prediction algorithm identified FEV1 (flow), DLCO (gas-exchange), FVC and VA (volume), FEF_{50} (small airways) and demographic data, which agrees well with previous publications [14–25,27,28]. One study [26] criticised the use of baseline lung function to predict \( V_{\text{O2MAX}} \). However, this study selected six prediction formulas from three papers [14,15,22] of which four included transplant candidates and one very severe COPD patients while the validation was done in 60 COPD-patients equally divided into GOLD 2, 3 and 4. Other papers have not challenged the possibility of predicting \( W_{\text{MAX}} \) or \( V_{\text{O2MAX}} \). However, Fregonezi [26] highlight a very important issue of all prediction models, i.e. generalisability, both related to disease severity and quality of assessment between centres.

The current study has a number of limitations. The prediction algorithm has been based on multicentre studies with high variability. Only one study was finally used as some of the key variables for prediction have not been collected in the other studies. A limitation with Random Forest is the non-intuitive relationship between the different variables making a judgement based on clinical knowledge important. In addition, Random Forest is usually applied to larger sample sizes. In the studies, the measurements of \( W_{\text{MAX}} \) and the demographic parameters were well documented but other good predictors had a lower quality or were missing (e.g. DLCO). The prediction algorithm does not account for differences in the level of activity among the patients, and whether the patients have little or much experience from bicycling. Also, the low number of patients in the pilot study makes the results from this study sensitive to the performance by individual patients.

Areas for further improvements of the prediction algorithm include QoL-variables, variables measuring daily activities, oxygen kinetic data and values from examinations of small airway functions such as impulse oscillometry measures. The possible role of hyperinflation as predictors in more severe patients should also be explored [35].

In summary, a prediction algorithm for \( W_{\text{MAX}} \) has been developed from incremental exercise bicycle tests in previously published multicentre clinical studies. The best predictors were FEV1 and DLCO. A new linear \( W_{\text{MAX}} \) test including the use of the prediction algorithm correlated well with the standard incremental \( W_{\text{MAX}} \) test. The new \( W_{\text{MAX}} \) test had a better correlation to the prediction algorithm, even though the algorithm was developed from the standard \( W_{\text{MAX}} \) test. In addition, an improved prediction algorithm with a slope closer to line-of-identity will benefit the new \( W_{\text{MAX}} \) test. Therefore, the new test will be utilized in future studies within our research project until the prediction algorithm has reached a level of precision that enables the \( W_{\text{MAX}} \) test to be replaced with a predicted value of \( W_{\text{MAX}} \).

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