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Prediction of peak oxygen uptake from 6-minute walk test in pulmonary hypertension

Paula Appenzeller[1,2], Fiorenza Gautschi[1,2], Julian Müller[1,2], Mona Lichtblau[1,2], Stéphanie Saxer[1,2], Simon R. Schneider[1,2], Esther I. Schwarz[1,2], Silvia Ulrich[1,2]*

[1]Clinic of Pulmonology, University Hospital Zurich, Zurich, Switzerland

[2]University of Zurich, Zurich, Switzerland

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***Correspondence:**

Prof. Dr. med. Silvia Ulrich
Clinic of Pulmonology
UniversityHospital Zurich
Rämistrasse 100
CH-8091 Zurich, Switzerland
Phone: ++41 44 255 22 20
silvia.ulrich@usz.ch

Abstract:

Maximal oxygen consumption (VO_{2max}) assessed by cardiopulmonary exercise training (CPET), is an important parameter for risk assessment in patients with pulmonary hypertension (PH). However, CPET may not be available for all PH-patients. Thus, we aimed to test previously published predictive models of VO_{2max} from the 6-minute walk distance (6MWD) for their accuracy and to create a new model.

We tested four models (Ross(2010), Miyamoto(2000) and Zapico et al.(2019)). To derive a new model, data was split into a training and testing dataset (70:30) and step-wise linear regression was performed. To compare the different models standard error of estimate (SEE) was calculated and the models have been graphically compared by Bland-Altman plots. Sensitivity and specificity for correct prediction into low risk classification (VO_{2max}>15ml/min/kg) was calculated for all models.

276 observations were included in the analysis (194/82 training/ testing dataset). 6MWD and VO_{2max} significantly correlated ($r=0.65$, $p<0.001$). Linear regression showed significant correlation of 6MWD, weight and heart rate response (HRR) with VO_{2max} and the best fitting prediction equation was: VO_{2max} = 1.83 + 0.031x6MWD(m) – 0.023xweight(kg) – 0.015xHRR(bpm). SEE for the different models were 3.03, 3.22, 4.36 and 3.08ml/min/kg for Ross, Miyamoto, Zapico et al. and the new model respectively. Predicted mean VO_{2max} was 16.5ml/min/kg (vs. observed 16.1ml/min/kg).

6MWD and VO_{2max} reveal good correlation in all models. However, the accuracy of all models is inadequate for clinical use. Thus, CPET and 6MWD measures both remain valuable risk assessment tools in the management of PH.

Introduction

Pulmonary Hypertension (PH) is a progressive disease, which may be idiopathic or associated to various conditions (1). PH is characterized by progressive narrowing of the pulmonary vasculature with consecutive increase in pulmonary arterial pressure, eventually leading to right heart failure and premature death (2). Patients with PH typically suffer from exercise limitation due to the inability to adequately increase the cardiac output even at early stages of disease. Measures of cardiorespiratory fitness can provide important information on the severity of functional impairment at diagnosis and are important to assess prognosis and response to therapies (3). Measurements of maximal oxygen uptake (VO_{2max}), obtained from cardiopulmonary exercise testing (CPET), stand in direct correlation with cardiac performance and thus reflect cardiorespiratory fitness (4, 5). VO_{2max} at physical exhaustion has shown to be a valuable diagnostic and prognostic tool for a variety of diseases (4) including PH (6, 7), for which it acts as an independent predictor of survival (8). However, correct measurement of VO_{2max} implies maximal effort of patients performing CPET and the performance of CPET may not be possible in everyday practice for some patients due to logistical reasons, patients' factors or contemporaneous assessment of other exercise parameters, such as the 6-minute walk distance (6MWD). Furthermore, CPET requires expensive equipment, trained health care professionals for conduction and interpretation of the test and is furthermore a time-consuming procedure.

Estimation of VO_{2max} from a simpler and widely available test, such as the 6-minute walk test (6MWT), has increasingly become a subject of interest, as it would provide a useful alternative to relatively complex CPET. The 6MWT is well established for patients with PH, is inexpensive, easy to perform, safe, well tolerated by the patients

(9) and has shown to be an important predictor of survival (10). Several studies have found a correlation between 6MWD and VO_{2max} in a variety of diseases (11-15). One of the first estimations of VO_{2max} from variables obtained in 6MWT in patients with advanced heart failure was proposed by Cahalin et al (13) in 1996, who found that the distance ambulated in the 6MWT could not only predict VO_{2max} but also short-term survival. Miyamoto et al.(16) have shown that the 6MWD correlates well to maximal CPET assessments, such as VO_{2max}, and acts as a strong independent predictor of survival in PH. However, they did not suggest a prediction equation. Ross et al.(14) has extracted regression equations from published scatterplots (e.g. from Miyamoto et al.(16)) and determined a generalized equation to predict VO_{2max} from mean 6MWD in a group of patients with diverse cardiovascular diseases. When looking specifically at PH, we only found one study by Zapico et al. (17) that has been suggesting a predictive model for VO_{2max} from 6MWD. They distinguished between three equations for children, adolescents and adults with primary PH. Predicting individual VO_{2max} would provide a useful and cost-effective tool for health professionals and researchers in the assessment and follow-up of PH patients, allowing easy insight into functional exercise capacity.

The aim of this study was to apply the equations proposed by Ross (14) (individual and generalized), by Miyamoto (16) (as determined by Ross et al. (14)), and by Zapico (17) to our own dataset and to compare them to a new multivariate predictive model for VO_{2max} based on our own set of patients with PH.

Methods

For this study, we used retrospective data from the PH-patient registry at the University Hospital in Zurich, Switzerland. All observations of VO_{2max} from January 2012 until May 2021 that coincided with a 6MWT within three months in stable PH-

patients of all diagnostic groups (mainly pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH)) without change in medication were included. To account for outliers and a potential ceiling effect (18, 19), observations with a 6MWD <200m or >650m and VO_{2max} <5ml/min/kg or >25ml/min/kg were excluded. There was no limitation to the number of observations per patient. All patients gave written informed consent and the Cantonal Ethics Review Board of Zurich gave their approval (BASEC Nr. 2021-01006).

Assessments

In our daily clinical setting, the 6MWT is routinely performed according to guidelines(9), walking back and forth in a hallway with 30m-markings. Standard procedures include measurements of blood pressure, heart rate and oxygen saturation before and at peak exercise. At the end of the test, modified BORG scale (1 to 10) is used to determine the rating of perceived exhaustion.

CPET is performed in a sitting position on a cycle ergometer and metabolic measurements are collected using breath-by-breath analysis, which is then averaged in a 30-second range. End exercise variables are defined as the mean of the final 30 seconds of exercise. Depending on the individual patient's fitness a ramp protocol with different watt increments is used (10/15/20 Watts per minute) to reach an approximate test duration of 10-12 minutes. All patients are instructed to cycle until exhaustion and measurements done according to international recommendations.(20) As this is a retrospective clinical study in patients with chronic right heart failure, plateauing of VO_2 max could not be verified in every patient and thus VO_2 at end-exercise was taken as VO_{2max} in accordance with the ATS statement.(20) The exercise protocols remained the same over the whole observation period.

Statistical analysis

Data was statistically analyzed using the program R (Version 4.0.1). All statistical test were two-sided at the 5% statistical significance level with the corresponding confidence intervals of 95%. Normality distribution was assumed in a sample size of n>30 and data was graphically inspected.

Applying existing regression models

As first, the relationship between VO_{2max} and 6MWD was graphically inspected for the entire dataset. Correlation was analyzed using Pearson correlation coefficient (*r*). We tested following four models for prediction of VO_{2max} from 6MWD:

1. Ross Mean; meanVO_{2max} = 4.948 + 0.023 x mean6MWD (m); (14)
2. Ross; VO_{2max} = 4.682 + 0.025 x 6MWD (m); (14)
3. Miyamoto; VO_{2max} = 4.213 + 0.026 x 6MWD (m); determined by Ross et al.(14) based on data published by Miyamoto et al. (16)
4. Zapico; VO_{2max} = -21.626 + 0.026 x 6MWD (m) + 4.103 x sex +0.174 x height (cm) – 0.071 x weight; (17)

Before further analysis, the data was randomly split at a 70:30 ratio into a training and a testing dataset(21), accounting for equal distribution of characteristics, such as 6MWD, gender, diagnosis and age. The training data set was used to determine a new predictive model, which was then, along with the other models, tested on the testing dataset.

Determining multivariate regression model

Step-wise linear regression was used to determine the variables to be included in the multivariate regression model. Tested independent variables were: age, weight, height, heart rate response during 6MWT (HRR, maximal exercise heart rate – heart

rate at rest), maximal heart rate and gender. If the slope of an independent variable was found to be significant ($p<0.05$), it was included in the multivariate regression model. Several models based on different methods were tested and compared, before choosing the best fitting model.

To compare the accuracy of the different models standard error of estimate (SEE) and its proportion of mean VO_{2max} was calculated and data was graphically analyzed. Bland-Altman graphs were used to visualize the difference between CPET results and the predictive models as two different approaches to determine VO_{2max}.

All models were tested on their ability to accurately classify patients into a low risk profile (correct classification into VO_{2max} >15ml/min/kg) using confusion matrixes, calculations of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Results

We could include 603 observations of VO_{2max} from the patient registry of the Zurich PH center. Of these, 261 observations had to be excluded due to missing coincident observations of 6MWD, 12 due to coincident change in PH-targeted therapy and 44 because 6MWD or VO_{2max} were not within the predefined range (6MWD <200 or >650 meters or VO_{2max} <5 or >25ml/min/kg). This resulted in 276 observations eligible for analysis (figure 1).

Characteristics for the training (n=194, 61% female) and testing (n=82, 71% female) dataset are shown in table 1. Both datasets showed a similar distribution of different diagnoses (PAH 60% vs. 61%, CTEPH 33% vs. 34% for training and testing dataset respectively). Mean age (mean±SD) was 59±14 years for the training and 58±15 years for the testing dataset. 6MWD (mean±SD) and VO_{2max} (mean±SD) were

504±85 meters and 15.3±3.8 ml/min/kg for the training, and 503±90 meters and 16.1±3.7 ml/min/kg for the testing dataset.

6MWD and VO_{2max} showed a significant correlation for the dataset overall (r = 0.65, p<0.001), which remains true for the training and the testing dataset (r = 0.69 and 0.59 respectively, both p < 0.001) (figure 2). Application of Ross's model to predict mean VO_{2max} for the whole dataset resulted in 16.5ml/min/kg (vs. 15.5ml/min/kg observed). The predictive equations by Ross, Miyamoto and Zapico et al. for individual VO_{2max} resulted in an SEE of 6.27, 6.30 and 7.62 ml/min/kg (40%, 41% and 49% of mean VO_{2max}) respectively when applied on the whole dataset.

Table 2 shows a comparison of the different prediction models. Coefficients, values for correlation (*r)* and p-values for Ross, Miyamoto, Zapico et al. were copied from the original publications (14, 16, 17). Based on our own data, we created a new model (R^2 = 0.48) with the regression equation 1.83 + 0.031 x 6MWD (m) – 0.023 x weight (kg) – 0.015 x HRR (bpm). When applied to the testing dataset SEE was 3.03, 3.22, 4.36 and 3.08 ml/min/kg (19%, 20%, 27% and 19% of mean VO_{2max}) for Ross, Miyamoto and Zapico et al., and the new model respectively. Predicted mean VO_{2max} using the generalized equation suggested by Ross et al. in the testing dataset was 16.5ml/min/kg (vs. 16.1±3.7 ml/min/kg observed).

Table 2 also provides information on sensitivity and specificity for the ability to correctly classify patients into a low risk profile (VO_{2max} >15ml/min/kg) in all models. Sensitivity ranged from 91-96% for the existing models and was 69% for our new model, while specificity ranged from 22-23% for the existing models and was 78% for our new model. The PPV was 63% for all existing models and 82% for our new model.

Figure 3 shows the graphical comparison between observed VO_{2max} in the testing dataset and predicted VO_{2max} for our new model and models of Ross, Miyamoto and Zapico et al.(14, 16, 17). Bland-Altman graphs comparing CPET and the predictive models as two approaches to determine VO_{2max} are shown in figure 4. For the new model, bias (95%-CI) was 1.08 (0.40 to 1.75)) ml/min/kg with an upper limit of agreement (ULoA) (95%-CI) of 6.89 (5.73 to 8.04) and a lower limit of agreement (LLoA) of -4.72 (-5.89 to -3.58). Bias, ULoA and LLoA were -1.12 (-1.77 to 0.46) ml/min/kg, 4.73 (3.60 to 5.85), -6.96 (-8.09 to -5.84) for the model of Ross et al. (14), -1.15 (-1.80 to -0.49) ml/min/kg, 4.7 (3.58 to 5.83), -7.00 (-8.13 to -5.88) for Miyamoto et al (16) and -2.34 (-3.18 to -1.49) ml/min/kg, 5.06 (3.60 to 6.52) and -9.74 (-11.20 to -8.28) for Zapico et al(17).

Discussion

The current analysis shows that the distance ambulated in the 6MWT and VO_{2max} were significantly correlated. The newly generated predictive equation and three previously published ones (14, 16, 17) were all able to predict VO_{2max} from demographics and the 6MWT with varying accuracy (SEE ranging from 3.03 to 4.36 ml/min/kg). Unfortunately, we judge this inaccuracy in the prediction of individual's VO_{2max} as insufficient for clinical use. With the new prediction model derived from our own dataset, we could markedly increase the specificity and PPV to predict a favorable VO_{2max} > 15 ml/min/kg from 6MWD compared to published equations.

Our new predictive model for determination of VO_{2max} from 6MWD and demographics revealed an SEE of 3.08ml/min/kg and thus showed similar accuracy as the published model of Ross et al. (14) with a SEE of 3.03ml/min/kg which was the most accurate from the tested equations. It seems that the model of Ross generally overestimates VO_{2max} in our population (see figure 3). Ross et al. based their

equation on a set of eleven populations with a mean 6MWD of 392m and mean VO_{2max} of 13.9ml/min/kg(14). In our dataset mean 6MWD is surprisingly high with 504m, corresponding to 94% of predicted reference values for 6MWD(22), while mean VO_{2max} (15.3ml/min/kg) still shows a relevant impairment of respiratory capacity. The large difference in walking distance compared to the smaller difference in VO_{2max} could explain why the models of Ross and Miyamoto, although having similar SEE (approximately 20% of mean VO_{2max}), overestimate individual's VO_{2max} in our dataset. The model of Zapico et al.(17), although being multivariate, shows less accurate prediction of VO_{2max} (SEE 4.36ml/min/kg, or 27% of mean VO_{2max}). They based their equation on a substantially younger population than our own, with a mean age of 27±6.7 years (vs. 59±14 years). However, despite similar mean VO_{2max} (16.03±6 ml/min/kg), mean 6MWD was again lower than in our own population (459±115 m) (17). Also compared to the French PH-registry, where the mean 6MWD was 329±109 m (23), or the UK registry where the mean 6MWD was 292.4±123 m (24), our study population showed a higher mean 6MWD which has already been previously shown in the Swiss Registry (25). It is known, that 6MWD shows a ceiling effect at higher values due to a general limitation in walking speed. Some studies suggest that this ceiling effect in PH-patients can be detected starting from 450m onwards (18, 26). A potential ceiling effect would suggest that variability in VO_{2max} would increase with increasing 6MWD. However, contrary to patients with chronic heart failure(15), where the 6MWD could not accurately predict VO_{2max} in patients with 6MWD >500m, in our population the correlation between VO_{2max} and 6MWD was moderate-good in observations with 6MWD >500m and only fair for <500m (r = 0.64, p<0.001 vs. r = 0.26, p=0.001) and showed less variability. This has already been previously established in patients with mild chronic heart failure(19), yet the reason remains unclear.

All of the models showed a SEE of over 3 ml/min/kg. While there is still little information about the minimal clinically important difference (MCID) for VO_{2max} in PH, rehabilitation was shown to improve VO_{2max} by 1.5ml/min/kg(27). Accordingly, the SEE of over 3ml/min/kg seems clearly above a MCID level and thus relevant, which suggests that the variation of all models for the individual VO_{2max}, as depicted by SEE, is too large for clinical use, and meaningful changes in true VO_{2max} might not be detected. As for 6MWD, the MCID is around 25-33m (27, 28), which would correspond to an increase in VO_{2max} of 0.83ml/min/kg as predicted by the model of Ross et al (14). In the Bland-Altman analysis all the models showed only a small bias ranging from -2.34 (-3.18 to -1.49) to 1.08 (0.40 to 1.75) ml/min/kg. Most of the measurements remain within the limits of agreement, which were defined as two times the standard deviation of mean differences, showing good agreement of the two models. However, as already established above, one can see that the models generally overestimate mean VO_{2max}. In addition, the upper and lower limits of agreement are too large, showing inadequate precision of the models.

We further examined whether the models, despite being unable to assess individual's VO_{2max} accurately, were able to classify patients correctly to low or high risk groups as defined by the PH risk stratification model, where a VO_{2max} of >15ml/min/kg classifies as low risk, and corresponds to an estimated 1-year mortality of <5%(29). The models of Ross, Miyamoto and Zapico (14, 16, 17) all showed high sensitivity (91-96%) but very low specificity (22-23%) supporting the claim, that these models overestimate VO_{2max} in our data, resulting in many falsely positive classifications to the low risk group, which would be very unfavorable for clinical use. Our own model had a sensitivity of 69% and specificity of 78%, suggesting a poorer predictive ability, but less false positive results than the other models, meaning less patients falsely classified to the low risk group.

Previous studies in patients with cardiac disease have shown that VO_{2max} cannot accurately be predicted from the 6MWT (30, 31). Ross et al. (14) found a SEE of 3.82ml/min/kg over a variety of diseases and exercise protocols, suggesting that predicting individuals VO_{2max} shows poor accuracy independent of underlying disease. Our results are in line with these findings and extend them to PH-patients. When we applied the generalized equation to predict the mean VO_{2max} of a population suggested by Ross(14) to our own data, the resulting mean was 16.5ml/min/kg, which is only 0.4ml/min/kg higher than the actual mean of 16.1ml/min/kg. Thus, this population mean equation is substantially more accurate than the prediction for individual VO_{2max} but has less clinical use.

Recent discussions have brought up the question, if it is clinically important to measure VO_{2max} in PH as drug studies showed contradicting results. Clinical trials leading to regulatory approval of most drugs to treat PH used the 6MWD as main outcome, whereas contemporary sequential, add-on drug combination therapy trials mainly used composite end-points(32). VO_{2max} as main outcome used in the Stride-1 study did not result a significant difference between PAH-patients treated with sitaxsentan vs. placebo, whereas the 6MWD as secondary outcome was different(33). Part of this discrepancy was attributed to the centers experience with CPET(11). In a recent multicenter randomized study, a standardized training program in PH resulted in significant improvements of both, 6MWD and VO_{2max}(34). Some of the discrepancy between 6MWD and CPET- measures may be attributed to experience of investigators and patients, time-lag between tests and other logistics, others may simply reflect that this two tests do not measures the same physiobiological process. However, due to the correlation between these two measurements, the 6MWD may still be used as a simple surrogate to VO_{2maxz}(35), even if its prediction has shown to be inaccurate.

A limitation of our study is that our population did include very few severely limited patients with a presumptively very low VO_{2max}, for whom a prediction equation would be more important as they may not be able to perform CPET due to the need of oxygen supplementation. Another limitation is that we included coincident observation ranging up to three months' time difference, rather than only including observations obtained on the same day. However, in clinical practice, performing several exercise test contemporaneously might not be possible and due to the retrospective nature of our data, we could not guarantee that the observations were actually from the same day. Further, we see a limitation in the fact, that some patients had several observations that were included in the analysis. It would have been interesting to include more CPET variables in the analysis, but our registry did not provide more detailed data.

Conclusion

Although the good correlation between 6MWD and VO_{2max} allows for the development of a predictive model based on regression equations, all proposed models show inadequate accuracy for clinical use in individual patients or classification into the low risk group. The prediction of mean VO_{2max} with the generalized equation proposed by Ross et al.(14) is highly accurate, also in the present study, which supports their statement, that the equation can be used to predict mean VO_{2max} in a population of patients from its mean 6MWD. While the 6MWT remains an important tool to assess prognosis and survival in PH, the 6MWD cannot be used to predict VO_{2max} for individual PH-patients and thus cannot replace CPET. Besides VO_{2max}, CPET allows for deeper insights into the underlying pathophysiological mechanisms of exercise limitation and can play a greater role in the diagnosis and management of PH.

Conflict of Interest Statement

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Author Contribution

P.A. and S.U. contributed to conception of design of the study, data acquisition, analysis and interpretation and drafting of the manuscript. E.S., F.G., J.M., M.L., S.S, S.S., S.U. contributed to the critical revision of the manuscript and provided final approval before publishing.

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Tables

Table 1. Characteristics of Training and Testing Dataset

	Training dataset	***Testing dataset***
Number of observations	194	82
Female,%	118 (61)	58 (71)
Diagnosis,%		
PAH	117 (60)	50 (61)
PH due to left heart disease	1 (1)	
PH due to lung disease	4 (2)	1 (1)
CTEPH	64 (33)	28 (34)
Miscellaneous	8 (4)	3 (4)
Haemodynamics at baseline		
mPAP at baseline, mmHg	42±4.1	39±13
PVR at baseline, mmHg	12±63	6±4
PAWP at baseline, mmHg	11±4	11±4
CI, ml/min/kg	2.8±0.8	2.9±0.7
Characteristics		
Age, years	59±14	58±15
Height, cm	169±11	169±10
Weight, cm	76±19	73±17
BMI, kg/m^2	27±5	25±5
NYHA functional class	2.2±0.7	2.2±0.6
6-minute walk test		
6-minute walking distance, m	504±85	503±90
At rest		
Systolic BP, mmHg	125±18	120±14
Diastolic BP, mmHg	79±12	78±12
Heart rate, bpm	84±14	84±12
Peripheral oxygen saturation, %	96±3	96±3
At peak exercise		
Systolic BP, mmHg	145±25	142±26
Diastolic BP, mmHg	83±14	82±13
Heart rate, bpm	121±21	121±22
Heart rate response, bpm	37±19	37±20
Peripheral oxygen saturation, %	89±9	90±7.8
BORG CR10, score	4.7±2	4.6±2
Cardiopulmonary exercise test		
VO_{2max}, ml/min/kg	15.3±3.8	16.1±3.7
Maximal workload, Watt	93±33	96±36

Data are given as mean(SD) or number(%).
PAH: pulmonary arterial hypertension, PH: pulmonary hypertension, CTEPH: chronic thromboembolic pulmonary hypertension, mPAP: mean pulmonary arterial pressure, PAWP: pulmonary arterial wedge pressure, CI: cardiac index, BMI: body mass index, NYHA: New York Heart Association, BP: blood pressure, VO_2: oxygen uptake

Table 2. Coefficients of different Linear Regression Models and Application to Testing Data

	Ross Mean (r = 0.82)		***Ross (r = 0.59)***		***Miyamoto (r =0.68)***		***Zapico (R^2 = 0.48)***		***New Model (R^2 = 0.48)***	
N of observations	1038		1083		27		82		194	
Parameters		p-values		p-values		p-values		p-values		p-values
Intercept	4.948	-	4.682	-	4.213	-	-21.626	-	1.83	0.248
6MWD, m	0.023	-	0.025	-	0.026	-	0.026	<0.001	0.031	<0.001
Sex	-	-	-	-	-	-	4.103	0.002	-	-
Height, cm	-	-	-	-	-	-	0.174	0.043	-	-
Weight, kg	-	-	-	-	-	-	-0.071	0.02	-0.023	0.22
HRR, bpm	-	-	-	-	-	-	-	-	-0.015	0.047
Applied to testing dataset										
SEE, ml/min/kg	-		3.03		3.22		4.36		3.08	
SEE%Mean	-		19%		20%		27%		19%	
Ability to classify to low risk (VO_{2max} >15ml/min/kg)										
Sensitivity	-		0.96		0.96		0.91		0.69	
Specificity	-		0.23		0.23		0.22		0.78	
PPV	-		0.63		0.63		0.63		0.82	
NPV	-		0.80		0.80		0.64		0.64	

r from correlation between VO_{2max} and six-minute walk distance, R^2 from linear regression of VO_{2max} against six-minute walk distance. 6MWD: six-minute walk distance, HRR: Heart Rate Response in 6MWT (heart rate at maximal exercise-heart rate at rest), SEE: Standard Error of Estimate, SEE%Mean: SEE as percentage of mean peak oxygen consumption. PPV: positive predictive value, PPN: negative predictive value. All coefficients, p-values and R^2 for Ross et al.(14) Myiamoto et al. (16) and Zapico et al. (17) are copied from the original publications.

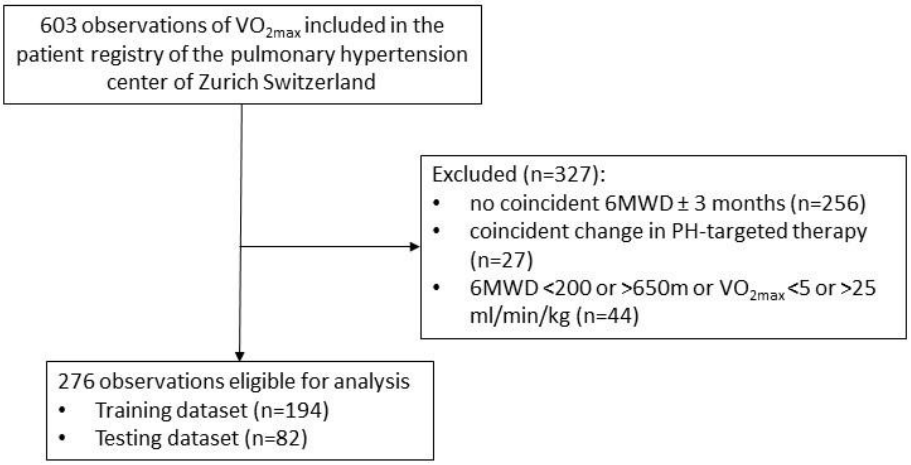
Figure Legend

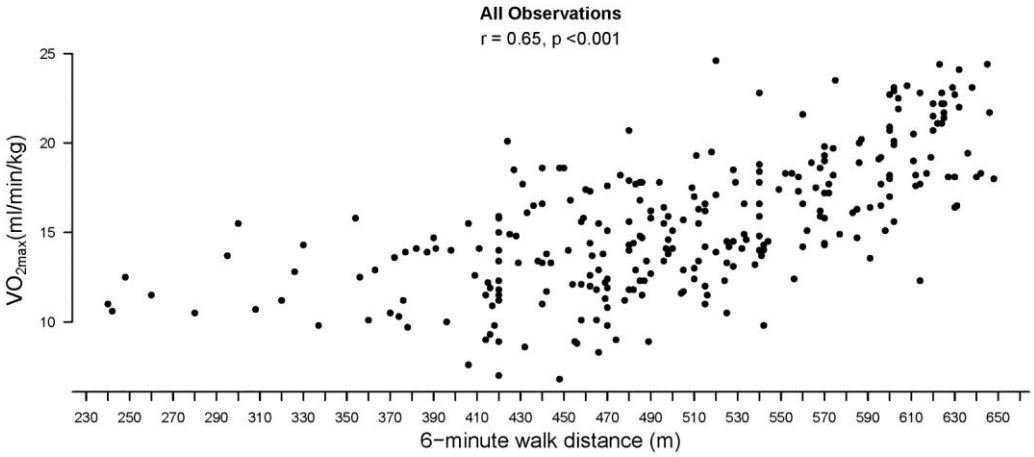
Figure 1. Patient's flowchart.

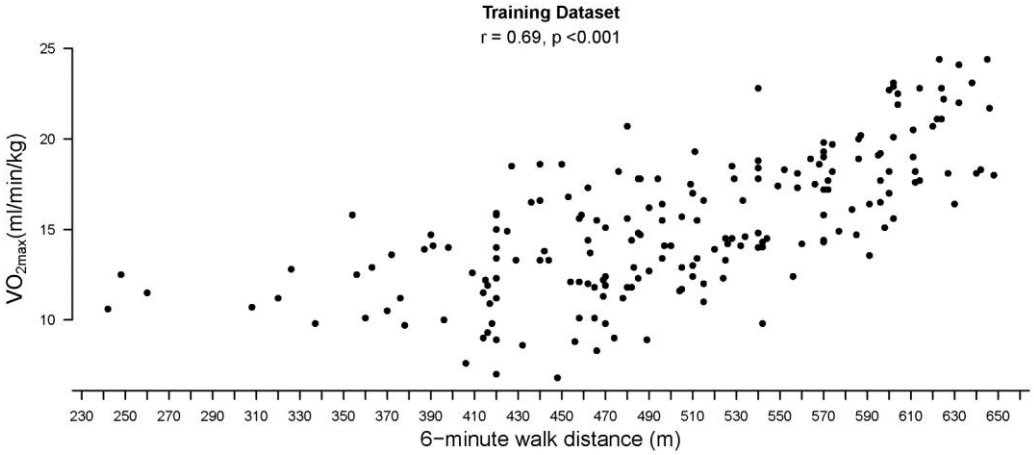
Figure 2. Correlation between 6-minute walk distance (m) and maximal oxygen uptake (maximal VO_2 (ml/min/kg)). The three panels show the correlation for all observations, the training and testing dataset respectively. Correlation coefficients (r) and p-values are given for all three datasets separately.

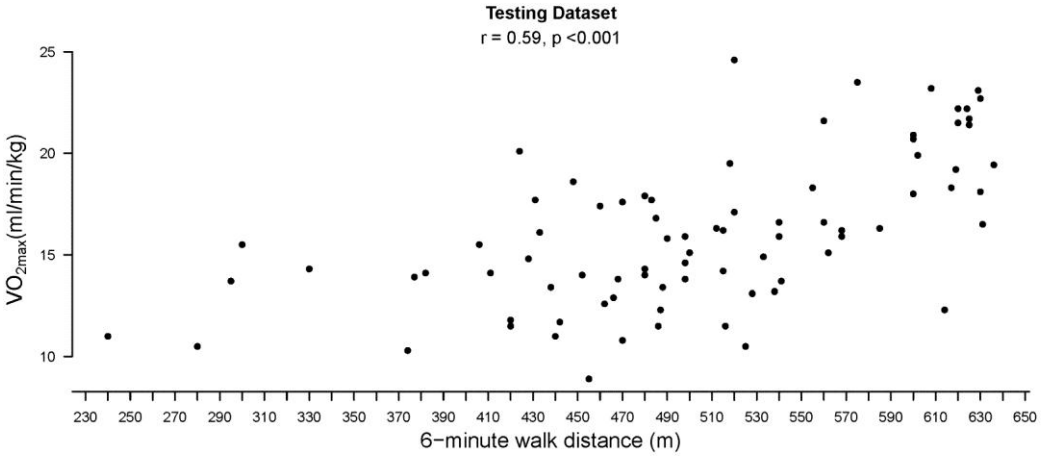
Figure 3. Comparison of predictive models. The panels show the predicted values for maximal oxygen uptake (maximal VO_2) against the 6-minute walk distance for each model separately. In each panel, the original data from the testing dataset is depicted for comparison. Standard error of estimate (SEE) for each model is shown below the panel headers. Mean VO_2 as determined by the generalized equation by Ross et al. (14) is shown in the corresponding panel.

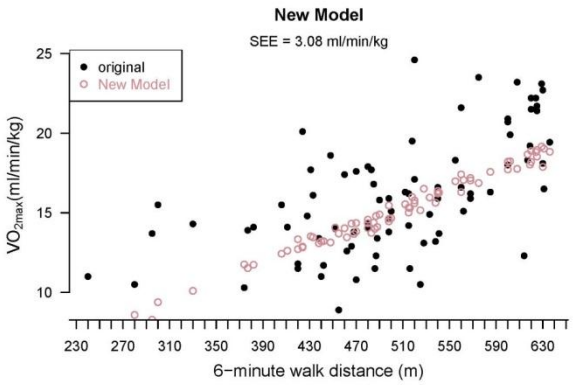
Figure 4. Bland-Altman graphs for the comparison of maximal oxygen uptake (maximal VO_2) determined by cardio pulmonary exercise testing (CPET) vs. using a predictive model based on 6-minute walk test (6MWT). The x-axis shows calculated the mean between the observed and the predicted values for maximal VO_2 (ml/min/kg) while the y-axis shows the difference between the two methods. The line corresponds to the mean difference in maximal VO_2 and the two dashed lines show the 95%-confidence interval. Each panel shows a different model as indicated by the panel's headers.

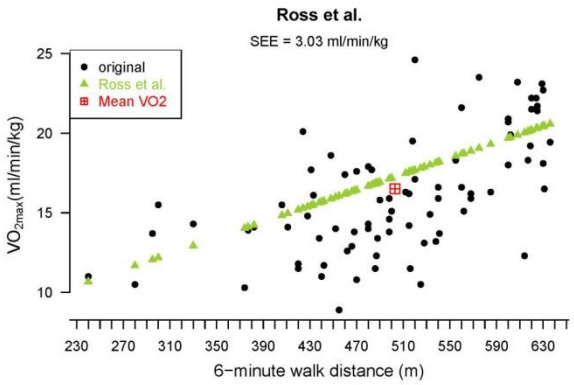

603 observations of VO_{2max} included in the patient registry of the pulmonary hypertension center of Zurich Switzerland
Excluded (n=327):
• no coincident 6MWD ± 3 months (n=256)
• coincident change in PH-targeted therapy (n=27)
• 6MWD <200 or >650m or VO_{2max} <5 or >25 ml/min/kg (n=44)
276 observations eligible for analysis
• Training dataset (n=194)
• Testing dataset (n=82)

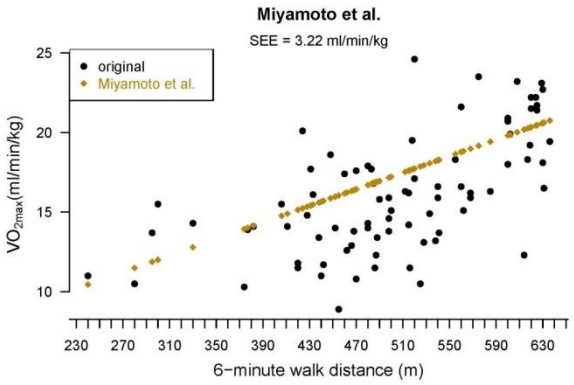

All Observations
r = 0.65, p <0.001
VO2max(ml/min/kg)
25
20
15
10
230 250 270 290 310 330 350 370 390 410 430 450 470 490 510 530 550 570 590 610 630 650
6−minute walk distance (m)

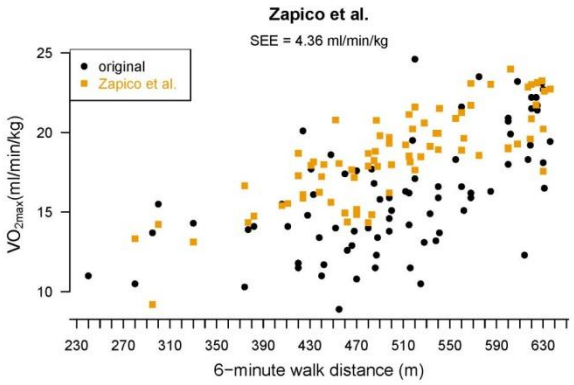

Training Dataset
r = 0.69, p <0.001
VO2max(ml/min/kg)
25
20
15
10
230 250 270 290 310 330 350 370 390 410 430 450 470 490 510 530 550 570 590 610 630 650
6−minute walk distance (m)

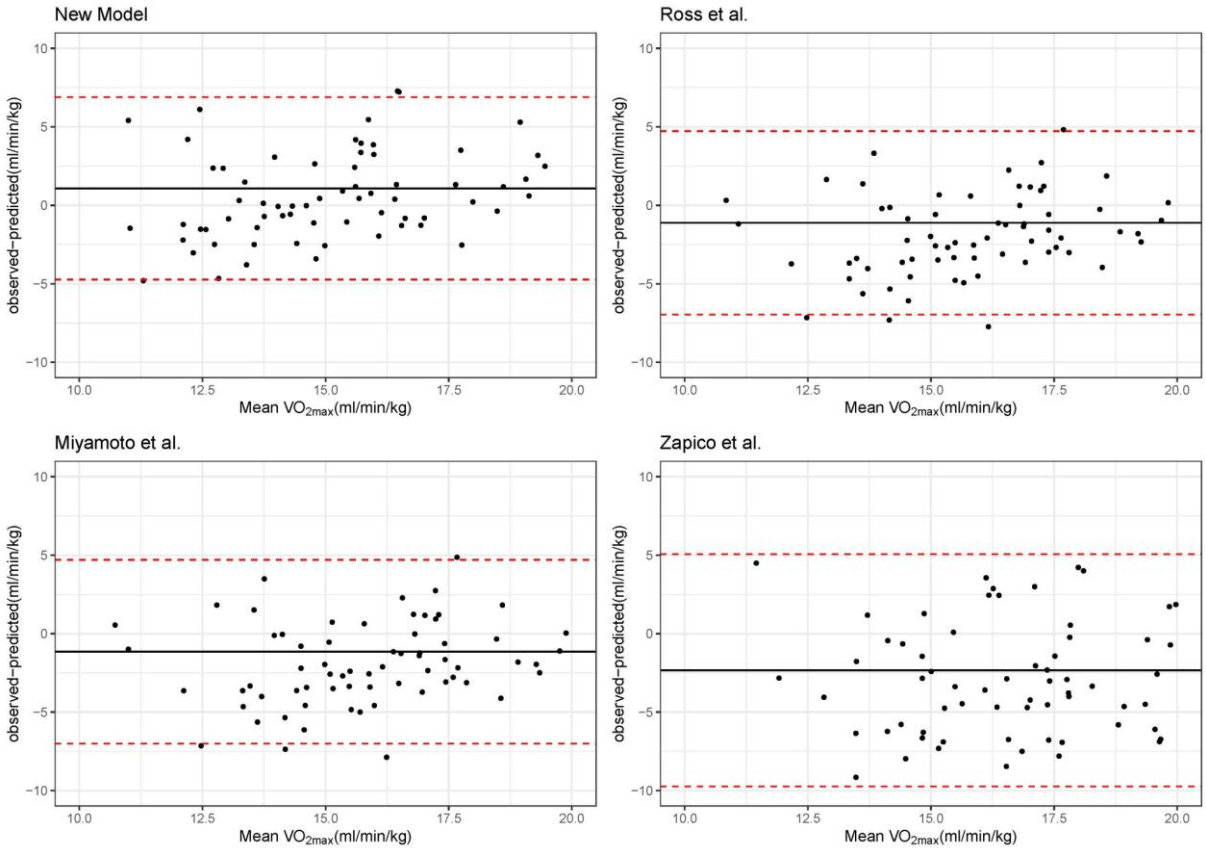

Testing Dataset
r = 0.59, p <0.001
VO2max(ml/min/kg)
25
20
15
10
230 250 270 290 310 330 350 370 390 410 430 450 470 490 510 530 550 570 590 610 630 650
6−minute walk distance (m)


New Model
SEE = 3.08 ml/min/kg
original
New Model
VO_{2max}(ml/min/kg)
6−minute walk distance (m)


Ross et al.
SEE = 3.03 ml/min/kg
original
Ross et al.
Mean VO2
VO_{2max}(ml/min/kg)
6−minute walk distance (m)


Miyamoto et al.
SEE = 3.22 ml/min/kg
original
Miyamoto et al.
VO_{2max}(ml/min/kg)
6−minute walk distance (m)


Zapico et al.
SEE = 4.36 ml/min/kg
original
Zapico et al.
VO_{2max}(ml/min/kg)
6−minute walk distance (m)


New Model
Ross et al.
Miyamoto et al.
Zapico et al.
observed−predicted(ml/min/kg)
Mean VO2max(ml/min/kg)
10
5
0
−5
−10
10.0
12.5
15.0
17.5
20.0