

The body weight-walking distance product as a superior parameter in determining the $\dot{V}O_2$ on-kinetics in coronary artery disease

Isadora S. Rocco

Universidade Federal de Sao Paulo

Walter J. Gomes

Universidade Federal de Sao Paulo

Hayanne O. Pauletti

Universidade Federal de Sao Paulo

Marcela Viceconte

Universidade Federal de Sao Paulo

Bruna C. Matos-Garcia

Universidade Federal de Sao Paulo

Rita Simone L. Moreira

Universidade Federal de Sao Paulo

Ross Arena

University of Illinois at Chicago College of Applied Health Sciences

Solange Guizilini (✉ s_guizilini@yahoo.com.br)

Universidade Federal de Sao Paulo <https://orcid.org/0000-0001-5453-2764>

Research article

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Abstract

Background The 6-minute walk test distance is frequently used to assess functional capacity of cardiac disease population. Nevertheless, anthropometric differences can confound or misestimate performance, which highlights the need for new parameters. This study aims to investigate the potential of the body weight-walking distance product (D.W), compared to 6-minute walk test distance, to predict exercise capacity measured by VO_2 on-kinetics in coronary artery disease (CAD) patients. **Methods** Cross-section study in a tertiary-care reference institution. Forty-six participants with multiarterial CAD with and without left ventricular dysfunction underwent a 6-minute walk test with simultaneous use of mobile telemetric cardiopulmonary monitoring to evaluate oxygen uptake (VO_2) on-kinetics and other cardiorespiratory responses. **Results** Perceived effort Borg for lower limb fatigue was only correlated with the D.W ($p=0.007$). The percent-predicted and actual distance were only modestly to moderately correlated with VO_2 on-kinetics ($p<0.05$). All the associations of VO_2 on-kinetics parameters were improved by showing a stronger correlation to the D.W ($p<0.0001$), which also had a larger effect size to identify differences between coronary disease patients compared to distance ($d = 1.32$ vs $d = 0.84$). **Conclusion** The D.W demonstrates potential as a measure superior to the distance in determining VO_2 on-kinetics in participants with CAD with and without left ventricular dysfunction.

Background

The gold standard to assess exercise capacity is the cardiopulmonary exercise testing, obtaining peak oxygen uptake (VO_2) through a maximal effort[1]. However, activities of daily living mostly require a submaximal level of exertion. Submaximal exercise testing performed with a constant load protocol, allows the evaluation of the VO_2 transition from rest to exercise, defined as VO_2 on-kinetics[2,3]. As with peak VO_2 , VO_2 on-kinetics has shown to be a significant prognostic marker in several chronic disease populations[4], especially in the coronary artery disease (CAD) with left ventricular systolic dysfunction (LVSD). In clinical practice, a number of field tests based on walking performance are frequently performed to assess the submaximal functional capacity in these patients[5].

The 6-minute walk test (6MWT) is easily administered and represents daily-life activities effort[6]. In a fashion similar to constant load ergometer testing, simultaneous use of mobile telemetric cardiopulmonary monitoring (MOB) while performing the 6MWT can provide the assessment of the VO_2 on-kinetics[7]. The mainly parameter obtained by the 6MWT is the distance in meters[8]. However, measurement of walking-distance has limitations in accurately predicting exercise capacity due to the presence of confounding factors (i.e. body weight, step length)[9] and also fails to provide clinical utilization for less impaired patients.

Chuang and Wasserman[10] have described a measurement of walking-work represented as the product of the body weight and distance(D.W). The D.W has been reported to better correlate with peak VO_2 and VO_2 at ventilatory threshold compared to walking-distance in patients with chronic obstructive pulmonary disease [10,11]. Nevertheless, to our knowledge, there is no current analysis that sustains whether the D.W

could be more effective than the 6MWT distance in assessing more accurately submaximal exercise capacity in CAD patients, beyond a severe impairment. Thus, the aim of the present study was to investigate the potential of the D.W, compared to 6MWT distance, to reflect variations in VO_2 on-kinetics in CAD patients with and without LVSD.

Methods

Study design

This cross-sectional study was conducted at the academic Hospital from a Federal University. Participants with a confirmed diagnosis of stable CAD were included in this study, which was approved by the Institutional Ethics Committee, in accordance with ethics' code of the Declaration of Helsinki. All patients were informed about the study and signed a written consent form.

CAD diagnosis was obtained by coronary angiography. Through echocardiography, a left ventricular ejection fraction (LVEF) $<45\%$ was used as a threshold to define participants with LVSD[12]. Exclusion criteria consisted of recent myocardial infarction (<6 months), presence of chronic or acute pulmonary disease, morbid obesity, neurological or orthopedic diagnoses impacting the ability to complete the study protocol, inability to comprehend and perform the tests or hemodynamic instability/severe arrhythmias during tests protocols.

6-minute walk test

Submaximal functional capacity was evaluated by the 6MWT, guided by the American Thoracic Society (ATS) recommendations[13]. Prior to the 6MWT, volunteers rested in a chair for 3–5 min to record baseline parameters. At the end of the 6MWT, participants again rested in the seated position for a recovery phase. Dyspnea and leg fatigue were rated by the perceived exertion Borg scale (PEB) before, after and every 2 min during the 6MWT. The highest distance achieved during the 6 minute test was recorded in meters. The D.W was calculated by multiplying the distance in kilometers (km) and body weight in kilograms (kg)[10]. The prediction equation proposed by Pereira e Soares ¹⁴ was used to predict walking distance for all participants.

MOB device during 6MWT

The 6MWT was performed with simultaneous MOB device (Oxycon Mobile-Viasys Healthcare, USA) to measure real time breath-by-breath cardiopulmonary responses[7]. The unit was harnessed to participants in a way that it had no effect on walking performance. Heart rate was recorded by a 12-lead electrocardiogram (Oxycon ECG module, Viasys Healthcare, USA). A facemask (with a dead space <70 ml) linked to a turbine volume transducer was used to continuously sample gas exchange, tidal

volumes and breathing frequency. Breath-by-breath calculations of VO_2 and carbon dioxide output (VCO_2) were digitized. Before each 6MWT, spirometry was performed with the MOB device according to ATS guidelines[15]. Steady-state variables were calculated as an average of the last 2 minutes of exercise. The transition of VO_2 through exercise was registered to obtain curve fitting of VO_2 on-kinetics.

Curve fitting of VO_2 kinetics

Raw breath-by-breath data obtained by the MOB device was preprocessed by the average of consecutive periods of 15 seconds. The fit of VO_2 on-kinetics was performed by a monoexponential regression model[2,16], as follows:

$$f(t) = y_0 + (y_1 - y_0)(1 - e^{-t/\tau})$$

where the $f(t)$ represents VO_2 at certain time (t); y_0 indicates the lower limit at $t=0$, i.e. the VO_2 at rest (the mean value of the last minute VO_2 prior to the test); y_1 represents the upper limit, indicating the VO_2 steady-state ($\text{VO}_{2\text{SS}}$); and τ indicates the time constant, i.e., the time needed to reach 63% of the $\text{VO}_{2\text{SS}}$. Since time delay was found to be undistinguishable from the second exponential phase[17], phase I was not modelled in this study. Whereas the time delay was not taken into account, the time needed for a 63% increase in $\text{VO}_{2\text{SS}}$, i.e. time constant (τ), also corresponds to the Mean Response Time (MRT). The MRT was corrected for the work rate ($w\text{MRT}$) during the 6MWT to avoid possible differences in intensity amongst participants. The work rate was obtained using the difference between VO_2 at rest and during effort ($\text{VO}_{2\text{SS}} - \text{VO}_{2\text{rest}}$)[18,19]. The quality of fit was assessed visually by two independent investigators to avoid data with obvious lack-of-fit, leading to 6 exclusions.

Statistical analysis

Categorical data were expressed in absolute and relative frequency and continuous variables were expressed as mean and standard deviation. The Shapiro-Wilk test was used to investigate normality distribution of data. Pearson correlation test was performed to investigate the relationship between VO_2 on-kinetics and 6MWT parameters. Comparison of 6MWT performance in CAD participants with and without LVSD was assessed by unpaired Student-t test or Mann-U-Whitney, according to data distribution. Cohen's d test was used to investigate the effect size of 6MWT parameters. A post hoc sample size analysis was performed to comprehend whether the effect size of 6MWT parameters would evolve with satisfying power of analysis. A p -value < 0.05 was considered statistically significant for all tests.

Results

The characteristics of the final forty-six volunteers' (**Fig 1**) are reported in **Table 1**. The VO_2 oxygen on-kinetics was successfully fitted, achieving an average of 3.8 ± 0.9 METS during the 6MWT, the mean of $\text{VO}_{2\text{SS}}$ was $909.8 \pm 23.7 \text{ ml}\cdot\text{min}^{-1}$, τ of 53.3 ± 9.12 seconds and $w\text{MRT}$ of $1.64 \times 10^{-3} \pm 1.0 \times 10^{-3} \text{ min}^2\cdot\text{ml}^{-1}$. All physiological responses to the 6MWT significantly changed at steady-state compared to rest, except for VE/VO_2 (**Table S1**).

The VCO_2 , METS, VE, the amount of change in VO_2 and PEB for dyspnea, were all significantly and positively-correlated to the 6MWT parameters (**Table 2**). However, all observed associations demonstrated a stronger relationship when the D.W was used. Notably, the PEB for lower limb fatigue was only found to be correlated with the D.W (**Table 2**).

The 6MWT distance was positively-moderately correlated with $\text{VO}_{2\text{SS}}$ ($R^2=0.36$, $p<0.0001$ – **Fig 2A**). The 6MWT percent-predicted distance was only positively-modestly correlated with $\text{VO}_{2\text{SS}}$ ($R^2=0.12$, $p=0.009$ – **Fig 2B**), while the D.W was strongly correlated with $\text{VO}_{2\text{SS}}$ ($R^2=0.67$, $p<0.001$ – **Fig 2C**).

The 6MWT distance had a negative-moderate association with $w\text{MRT}$ ($R^2=0.29$, $p<0.001$ – **Fig 2D**). The correlation between 6MWT percent-predicted distance and the $w\text{MRT}$ was negatively-moderately correlated ($R^2=0.22$, $p=0.003$ – **Fig 2E**), whereas the $w\text{MRT}$ association was improved by showing a negatively-strong correlation to the D.W ($R^2=0.49$, $p<0.001$ – **Fig 2F**).

There was a stronger positive correlation between D.W and LVEF compared to the walking distance or to the % predicted distance ($r=0.72$, $p<0.001$ vs $r=0.55$, $p=0.001$ or $r=0.43$, $p=0.005$, respectively). When participants were dichotomized according to LVEF, those with LVSD (LVEF<45%) had worse submaximal functional capacity measures compared to participants without LVSD (LVEF >45%). Participants with LVSD achieved a lower 6MWT distance and lower D.W (**Table 3**). The effect size Cohen d' test demonstrated that D.W was superior in identifying the difference between the groups compared to 6MWT distance and percent-predicted distance ($d=1.32$ vs $d=0.84$ and $d=0.02$, respectively – **Table 3**). Also, because of a large effect size was founded when D.W was used, the analysis of group comparisons achieved a power of 95% (**Table 3**).

Discussion

The current study demonstrates that the D.W had a better relationship with VO_2 on-kinetics compared to 6MWT-distance and percent-predicted distance in patients with CAD. Moreover, the D.W had a larger effect size than the 6MWT distance in CAD patients with and without LVSD. These findings support the premise that the D.W is an easily applying and potential meaningful measure, in the context of quantifying submaximal exercise performance and physiologic health during exertion, even in patients with less severe impairment.

Field tests have been used to assess exercise capacity in chronic disease populations for a number of years. Submaximal exertion tests enable a greater patient toleration and perhaps had a stronger

indication of the ability to perform daily activities[20]. In this context, the 6MWT has been used as a prognostic marker for several diseases, as in cardiac patients, especially in those with LVSD[6,21,22]. Nevertheless, the 6MWT-distance alone is only able to detect the presence of a marked exercise limitation, i.e. in patients unable to walk more than 300 meters. In order to acquire physiological insight, several research groups around the world have simultaneously employed a MOB device during the 6MWT[18,19,23]. The breath-by-breath analysis of cardiopulmonary responses more accurately quantifies physiologic health and of the degree of an exercise limitation. Furthermore, the analysis of VO_2 during the initial phase of the 6MWT allows for the assessment of VO_2 on-kinetics, as in our study, which is linked to the risk for future adverse events[19,24].

The walking distance in meters had historically been recognized as the primary variable obtained with the 6MWT. Several studies report threshold 6MWT-distance values to predict increased risk of adverse events such as myocardial infarction, stroke, re-hospitalization and mortality[25]. Despite its greater utilization, studies reported only a moderate association between the 6MWT-distance and peak VO_2 and other cardiopulmonary exercise testing parameters[8]. In fact, we also found a moderate relationship between 6MWT-distance with VO_{2SS} and wMRT in our CAD patients, explaining the discrepancy from the previously known relation between METS and walking-speed. This finding could suggest that the use of the 6MWT-distance is only able to predict an obvious impairment of functional capacity and then an already very predictable risk of morbidity and mortality.

Additionally, predicted values based on age, gender and body mass index have been studied for populations around the world to obtain normative values of performance. Since reference values are acquired in each country separately, it can be difficult to apply this as a worldwide parameter. Moreover, in the current study, only a modest association was found with VO_2 on-kinetics when the percent-predicted values of the 6MWT were used. The lack of a stronger relation could indicate that the functional contribution of participants' body processes during exercise is not well represented by current prediction models.

The current limitations in the physiological information derived from the 6MWT encourage the search of new parameters that more accurately reflect functional performance[9] and an overall health status. Previous reports have already indicated that the work of walking during the 6MWT can be correlated with the horizontal work on a treadmill (W_{H0}). Since the 6MWT is performed in a horizontal plane and at constant velocity, the work of walking in the 6MWT can be calculated as a product of distance and weight (i.e., $D.W$)[10]. In our study, we found that all associations with cardiorespiratory responses were greatly improved when the $D.W$ was used rather than walking and percent-predicted distance values. We observed a moderate to modest correlation between both VO_{2SS} and wMRT with walking and percent-predicted distance. However, when the $D.W$ was applied, a strong correlation was observed with VO_{2SS} ($r=0.82$, $p<0.001$) and wMRT ($r=-0.70$, $p<0.001$). These results corroborate with other findings in the literature; Chuang, Lin and Wasserman[10] found a modest correlation between 6MWT-distance and peak VO_2 ($r=0.40$, $p<0.05$) *versus* a stronger correlation between $D.W$ and peak VO_2 ($r=0.67$, $p<0.05$). Similarly,

Poersch et al[11] found that peak VO_2 was modestly correlated with distance ($r=0.32$, $p=0.084$) and percent-predicted distance using Soares and Pereira[14] equation ($r=0.35$, $p=0.058$), while strongly correlated with D.W ($r=0.76$, $p<0.01$). Both aforementioned studies were performed in chronic obstructive pulmonary disease cohorts that underwent cardiopulmonary exercise testing. To the best of our knowledge, this is the first study to evaluate the association between D.W of the 6MWT with VO_2 on-kinetics in CAD patients.

It is already well established that CAD exposes the myocardial to a mismatch in oxygen supply and demand. As the time associated with this imbalance elongates, CAD evolves with greater manifestations, leading to a greater impairment in ventricular function, as in LVSD. CAD is the major cause of chronic heart failure leading to progressive degrees of impaired exercise capacity[26]. A limitation of physical activity in this population can be detected by a lower 6MWT performance[6]. In the current study, the LVEF was moderately to strongly correlated to all three 6MWT parameters evaluated in our CAD cohort. As expected based on previous literature[22], our results also revealed that when participants were separated according to LVEF, those with LVSD achieved lower distance and lower D.W during the 6MWT.

In the present study, despite the 6MWT distance already had a large effect size ($d=0.84$), the D.W effect size was much larger ($d=1.32$), indicating this as a powerful parameter to discriminate the level of disease impairment. These findings suggest that D.W may be a preferred measure in quantifying submaximal performance. Moreover, the stronger correlation observed to VO_2 on-kinetics support the widespread use of D.W, particularly if ventilatory expired gas analysis is not available.

A limitation of this study was that most of the participants were males (80.4%). Women exhibit a lower exercise capacity and as such a gender bias might impact results, especially due to the utilization of a walking test[27,28]. This was a cross-sectional study with a modest number of patients. Future research is necessary to established specific D.W values that could predict clinical outcomes in cardiac patients and reinforced this as superior to walking distance.

Conclusions

The D.W demonstrates potential as a measure superior to the 6MWT distance in determining VO_2 on-kinetics in participants with CAD. The D.W seems to reflect the work of walking and may be a stronger parameter for evaluation of submaximal exercise capacity and performance, especially if a cardiopulmonary testing device is not available.

Abbreviations

6MWT: 6-minute walk test; BMI: body mass index; D.W: body weight walking product; CAD: coronary artery disease; CPX: Cardiopulmonary exercise testing; CRF: cardiorespiratory fitness; CVD: cardiovascular disease; LVSD: left ventricular systolic dysfunction; LVEF: left ventricular dysfunction; MOB: mobile

telemetric cardiopulmonary monitoring; NYHA: New York Heart Association; PEB: perceived exertion Borg scale; VO_2 : oxygen uptake; VT: Ventilatory threshold

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contribution

I. Rocco contributed to study design, collection and analysis of data and drafting the paper; H.O. Pauletti, B.C. Matos-Garcia and M Viceconte contributed to collection of data; Rita Simone L. Moreira to technical aspects of the ethics and methodology; W.J. Gomes, R. Arena and S. Guizilini contributed to study design and drafting of the paper.

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Ethics approval and consent to participate

The study was approved by the Human Studies Committee of the Federal University of Sao Paulo, and all subjects gave written informed consent.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1: Demographic and clinical characteristics of volunteers

Variable	n=46
Age (years), mean (SD)	60.2 (7.6)
Sex (M/F)	37/9
Weight (kg), mean (SD)	70.06(10.45)
BMI (kg/m ²), mean (SD)	26.25(8.26)
Hypertension (%)	82.3
Diabetes (%)	32.3
LVEF, mean (SD)	0.51(0.15)
Main affected artery (%)	
LAD	46.35
RCA	39.65
Cx	1.05
Others	12.95
6MWT (m), mean (SD)	441(67)
%Predicted-distance, mean (SD)	82.1(11.3)
D.W (km.kg ⁻¹), mean (SD)	30.9(67.9)

Body mass index; LAD, Left anterior descending artery; Cx, Circumflex artery; LVEF, Left ventricular ejection fraction; RCA, Right coronary artery; SD, standard deviation; 6MWT, 6-Minute Walk Test; BMI.

Table 2. Different 6MWT parameters in relation to submaximal exercise performance.

	Distance (m)		% predicted		D.W	
	<i>r</i>	<i>p value</i>	<i>r</i>	<i>p value</i>	<i>r</i>	<i>p value</i>
ΔVO_2 (ml.min ⁻¹)	0.61	<0.001	0.36	0.034	0.74	<0.001
VCO_2 (ml.min ⁻¹)	0.63	<0.001	0.37	0.029	0.79	<0.001
RER	0.13	0.44	-0.008	0.96	0.21	0.24
METS	0.67	<0.001	0.48	0.004	0.69	<0.001
VE (L.min ⁻¹)	0.54	0.001	0.29	0.09	0.69	<0.001
VE/ VCO_2	-0.28	0.10	-0.23	0.19	-0.22	0.21
BR (%)	-0.10	0.57	0.05	0.75	-0.27	0.14
Δ PEB, dyspnea	0.38	0.030	0.35	0.045	0.44	0.012
Δ PEB, limb fatigue	0.21	0.23	0.17	0.35	0.45	0.007

The Pearson's correlation test was used to investigate the associations. Δ , amount of change from rest to the steady-state; VO_2 , oxygen uptake; VCO_2 , carbon dioxide output; RER, respiratory exchange ratio; METS, metabolic equivalents; VE, minute; VE/ VCO_2 , ventilatory equivalent of carbon dioxide; BR, breathing reserve; PEB, perceived effort Borg scale.

Table 3: 6MWT parameters to differentiate subjects according to absence or presence of LVSD.

	LVEF>45% (n=24)	LVEF<45% (n=22)	Power	Effect size &	d lower limit	d upper limit
Distance(m)	463.7 (62.9)	412.3 (62.6)*	0.51	0.84	-24.32	27.01
% predicted	82.2 (9.1)	81.9 (13.9)*	0.01	0.02	-3.64	5.84
D.W(km.kg ⁻¹)	34.26 (6.25)	27.05 (4.77)*	0.96	1.32	-1.19	3.31

Values are mean (standard deviation). D.W, body weight-walking distance; LVEF, Left ventricular ejection fraction; 6MWT, 6-minute walk test. *p<0.01 to comparison between groups. & Cohen' d effect size.

Figures

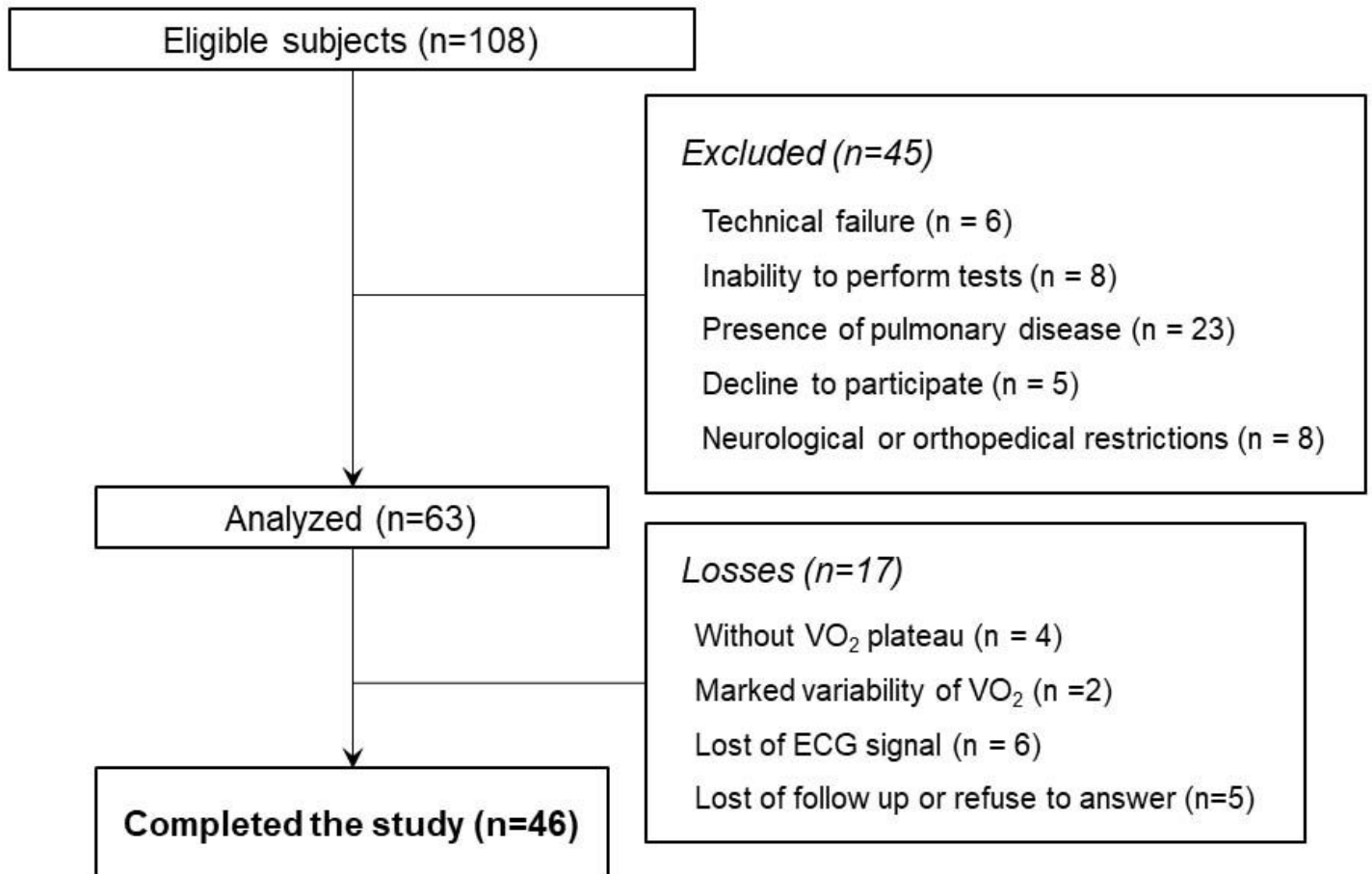


Figure 1

A flow-chart of study evaluation protocol.

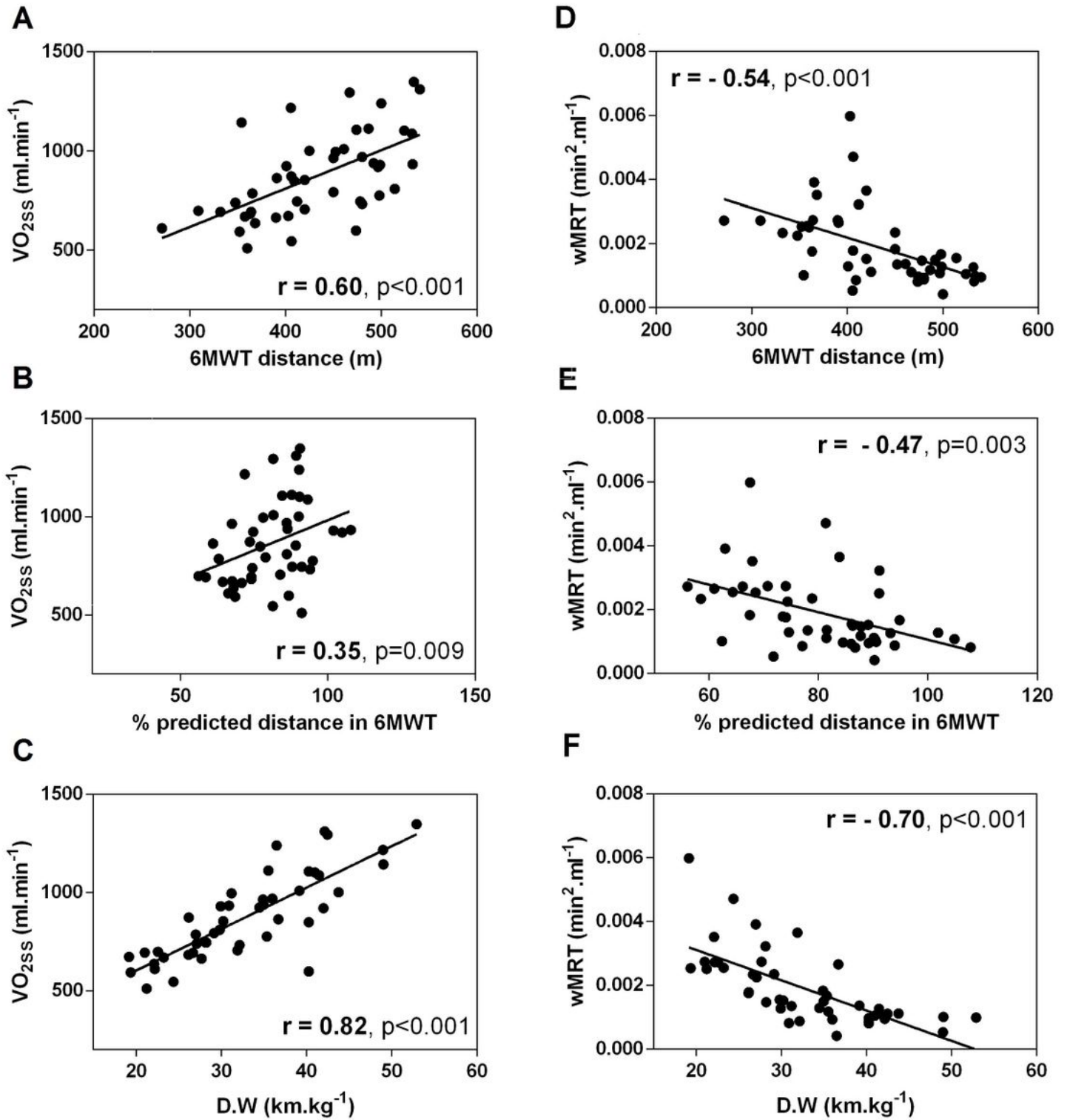


Figure 2

Pearson's correlation test to investigate association of VO_{2SS} and wMRT in relation to 6MWT parameters. 6MWT, 6-minute walk test; D.W, body weight-walking distance product; VO_{2SS} , oxygen

uptake at steady-state.

Supplementary Files

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- [TableS1.doc](#)