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Cross-Sectional study

Development of a multivariate model of the six-minute walked distance to predict functional exercise capacity in hypertension

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ABSTRACT

Background: Hypertension is associated with deterioration of musculoskeletal function and functional capacity. Existing prediction models for assessment of the 6-min walk test (6MWT) do not capture the disease-related functional capacity. This study developed a multivariate prediction model of the measured 6-min walked distance ($6MWD_M$) in hypertension and proposed target-values based on optimal therapeutic aims.

Methods: Seventy-six patients (38 men, 56.1 ± 14.3 years, systolic pressure 156.7 ± 17.5 mmHg, diastolic pressure 92.9 ± 6.9 mmHg) underwent anamnesis, physical examination, and laboratory analysis. Functional capacity was assessed using the 6MWT, being the $6MWD_M$ considered as the dependent variable. Independent variables included sex (*S*, coded 'male' = 1, 'female' = 0), age (*A*), body height (*H*), body mass, mean blood pressure (*MBP*), and physical activity (*IPAQ*, coded 1–5). Target-values were derived from theoretical scenarios of optimal blood pressure and physical activity, separately and combined.

Results: Patients walked 324.5 ± 10.1 m in the average of two trials 30-min apart. Pearson's correlation coefficient showed moderate-to-weak significant associations between $6MWD_M$ and all independent variables. The final multivariate model was $6MWD_P = 611.347 - 4.446 \times MBP + 267.630 \times H - 1.511 \times A + IPAQ_{code} + S_{code}$ (adjusted $R^2 = 0.680$, SE of bias = 6.3 m), suggesting that clinical, anthropometric, and hemodynamic information determines functional capacity. Predicted values yielded a group-average of 325 ± 87 m. Target-values under the optimal scenario resulted in 420 ± 60 m.

Conclusions: Sex (men), higher body height, higher physical activity, lower mean blood pressure, and lower age are independently correlated with higher $6MWD_M$ in patients with hypertension. Target-values can be estimated for therapeutic aims related to hemodynamics and lifestyle.

1. Introduction

Hypertension is a major risk factor for cardiovascular diseases (Mancia et al., 2013). The pathophysiology of hypertension includes endothelial dysfunction and vascular remodeling (Ferreira et al., 2012; Hernández et al., 1999; Liao et al., 1999). Ultimately, hypertension leads to target-organs damage (Mancia et al., 2013) and impaired skeletal muscle function (Ferreira et al., 2011; Hernández et al., 1999). Hypertension is also associated with deterioration of functional capacity to perform daily living activities (Hajjar et al., 2007). As apparent for other systemic diseases – e.g. sickle cell anemia (Marinho et al., 2016) – patients with hypertension also present limited functional exercise capacity, depending on the presence of comorbidities and baseline blood pressure (Ramos and Ferreira, 2014). Therefore, there is a need for an early identification of limited functional capacity both for delaying the disease progression and prescription of cardiac rehabilitation programs.

The assessment of functional capacity using the 6-min walk test (6MWT) is gaining increased interest in the cardiovascular field (Guyatt et al., 1985). The 6MWT is an effective test for the assessment

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of functional capacity, is easy to administrate, safe, inexpensive, valid, and reliable in patients with cardiovascular diseases (Bellet et al., 2012; Butland et al., 1982; Papathanasiou et al., 2013). The measured distance ($6MWD_M$) is the direct outcome of the 6MWT; predict values ($6MWD_P$) are estimated from indirect methods such as models obtained from healthy populations (Casanova et al., 2011). However, the external validity of these models is compromised due to differences in the empirical distributions of dependent and independent variables, but also to between-variables correlations (Toutenburg and Shalabh, 2009). Therefore, the current trend for developing prediction models of $6MWD_M$ uses data from patients to develop a population-specific predictive model (Canning et al., 2006; Deuschle et al., 2011; Falvo and Earhart, 2009a, 2009b). In addition, none of those models were validated for patients with hypertension (Casanova et al., 2011).

Models obtained from international (Salbach et al., 2015) and Brazilian (Britto et al., 2013; Dourado et al., 2011; Iwama et al., 2009; Soares and Pereira, 2011) healthy samples have few relevant predictors are included in the model as suggested from their low coefficients of determination. Sex, age, body height are risk factors for cardiovascular diseases and also common predictors of $6MWD_M$ (Mancia et al., 2013; Parker et al., 1998). In addition, the $6MWD_M$ is correlated to hemodynamic variables in hypertension (Ramos et al., 2014). Although physical activity is an independent predictor in healthy older females (Steffens et al., 2013), its role as a $6MWD_M$ predictor in hypertension remains uninvestigated. Therefore, this study aims at developing a population-specific, multivariate prediction model with target-values of $6MWD_M$ in hypertension.

2. Methods

2.1. Ethics

This research was conducted in accordance with the Declaration of Helsinki and received approval by the Research Ethics Committee at the Centro Universitário Augusto Motta (CAAE 05517012.8.0000.5235). Participants signed a written informed consent form after being verbally explained about the study aims and procedures.

2.2. Study design and sample size

This cross-sectional study (Fig. 1) followed the *T*ransparent *R*eporting of a multivariable prediction model for *I*ndividual *P*rognosis or *D*iagnosis (Collins et al., 2015) and recommendations for rehabilitation research (Seel et al., 2012). The sample size was determined for the major outcome of this study based on the ratio between predictors and participants to allow the required number of events for multiple linear regression analysis. The minimum ratio 1:10 of predictor:participant was considered to develop the regression model as recommended for multiple regression linear models (Babyak, 2004).

A single examiner (physiotherapist with specialization in cardiac rehabilitation) performed all screening assessments for checking the compliance with the inclusion and exclusion criteria. The same assessor performed all other clinical and functional assessments at morning (9–11 a.m.) and was not blinded to the participants' demographic characteristics because the $6MWD_M$ is not likely to be influenced by this information.

2.3. Recruitment of participants and eligibility criteria

Seventy-six patients undergoing routine antihypertensive medication therapy were prospectively assessed for eligibility at the Division of Arterial Hypertension (RJ, Brazil) (Table 1). Inclusion criteria comprised age >18 years and the diagnosis of primary systemic arterial hypertension, characterized as systolic blood pressure (SBP) > 140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg on repeat visits (Mancia et al., 2013). Additional criteria included no physical limitations that influence walking, no

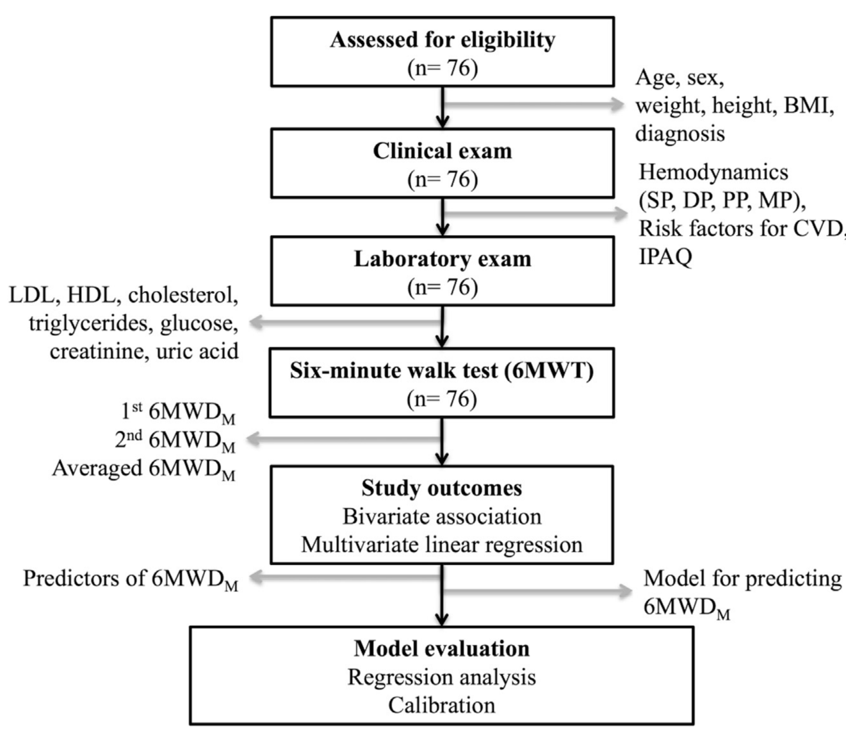

Fig. 1. Study flowchart.

recent history (<6 months) of musculoskeletal pain in the lower limbs and spine, and no heart valvular disease, ventricular dysfunction, nor cardiac arrhythmias.

2.4. Clinical assessment

Clinical history and physical examination were performed after a 10-min rest in the sitting position according to international guidelines (Mancia et al., 2013). Self-reported information was collected about the duration of hypertension, smoking habits, and history of premature cardiovascular disease (men <55 years, women <65 years). Body height and body mass were obtained using an analog scale and were used to calculate the body mass index. Physical activity was assessed using the short-version of the International Physical Activity Questionnaire (IPAQ, Portuguese language) (Matsudo et al., 2012).

SBP, DBP and heart rate (HR) were obtained at the office using an oscillometric-automated device positioned at the right-sided wrist (BP3AF1-3; Onbo Electronic, Shenzhen, China), spaced by a 1–2 min interval. Pulse pressure (PP=SBP-DBP) and mean blood pressure (MBP = DBP + PP/3) were also calculated. Blood pressure values were reported as the average of the three measurements. Hypertension grade was determined according to the averaged blood pressure values (Mancia et al., 2013).

The following cardiovascular risk factors were evaluated: obesity (body mass index ≥30 kg m^{-2}), sedentary lifestyle (IPAQ = sedentary or irregularly active during the prior month) (Mancia et al., 2013), dyslipidemia (low-density lipoprotein-cholesterol >70 mg dl^{-1}, high-density lipoprotein-cholesterol <50 mg dl^{-1} and triglycerides >150 mg dl^{-1}) and diabetes mellitus (fasting serum glucose >126 mg dl^{-1}) (American Diabetes Association, 2014).

Table 1
Sample characteristics.

Variable	Values
Female:Male, *n* (%)	38:38 (50:50)
Age (years)	56.1 ± 14.3 [19; 85]
Body Height (m)	1.72 ± 0.07 [1.53; 1.92]
Body Mass (kg)	85.4 ± 13.9 [56.0; 134.2]
Body mass index (kg/m^2)	28.7 ± 4.2 [18.9; 40.1]
Hypertension course (months)	86.4 ± 83.1 [1; 420]
Classification of hypertension, n (%)	
Optimal	1 (1.3)
Normal	3 (3.9)
High normal	15 (19.7)
Stage-I	51 (67.1)
Stage-II	6 (7.9)
Office blood pressure (mmHg)	
Systolic	156.7 ± 17.5 [100; 186]
Diastolic	92.9 ± 6.9 [60; 110]
Mean arterial pressure	114.2 ± 9.0 [80.0; 126.7]
Pulse pressure	63.8 ± 15.5 [30; 94]
Risk factors, n (%)	
Smoker	20 (26.3)
Sedentary	48 (63.2)
History of premature CVD	28 (36.8)
Obesity	25 (32.9)
Dyslipidemia	61 (80.3)
Diabetes mellitus	23 (30.3)
Physical activity level	
Very active (=5)	4 (5.3)
Active (=4)	22 (28.9)
Irregularly active A (=3)	15 (19.7)
Irregularly active B (=2)	35 (46.1)
Not active (=1)	0 (0)
Antihypertensive drug treatment, n (%)	
Diuretic	75 (98.7)
Vasodilator	41 (53.9)
β-Blocker	12 (15.8)
ACE inhibitor	12 (15.8)
Sympatholytic	70 (92.1)
AT2 antagonist	1 (1.3)

Mean ± SD [minimum; maximum] or frequency (%). ACE - angiotensin-converting enzyme; AT2 – angiotensin 2; CVD - cardiovascular disease.

Table 2
Result of the 6-min walk test in patients with hypertension.

Variable	Class	Values
Six-minute walked distance (m)		
	Test no. 1	333.7 ± 103.2
	Test no. 2	315.6 ± 106.0
	p value	0.001
	Test No. 2–1 (%)	−5.3 ± 11.0
	Average 6MWD$_M$	324.7 ± 101.4 [142; 620]
Heart rate (beats/min, %)		
	Rest	90.4 ± 6.9 (53.9 ± 5.8)
	1st minute	110.3 ± 13.5 (65.7 ± 9.5)
	6th minute	97.8 ± 10.8 (58.2 ± 7.8)
Systolic pressure (mmHg)		
	Rest	156.7 ± 17.5
	1st minute	174.1 ± 18.4
	6th minute	164.8 ± 17.7
Diastolic pressure (mmHg)		
	Rest	92.9 ± 6.9
	1st minute	104.9 ± 9.4
	6th minute	96.1 ± 7.3

Mean ± SD [minimum; maximum].

2.5. Assessment of functional capacity (direct method)

The 6MWT was performed according to international guidelines (Crapo et al., 2002) with a minor adaptation regarding the corridor length (Ramos et al., 2014; Ramos and Ferreira, 2014). The 6MWT was performed along an 18-m linear corridor delimited with traffic cones at both ends. Participants were instructed to walk as far as they could along the corridor and were allowed to slow down their walk or to interrupt it if necessary. Participants were monitored verbally by the Borg modified scale every 2 min. By the sixth minute, each participant was requested to stop and the number of runs and the remaining distance of the last run were annotated to calculate the 6MWD$_M$. Blood pressure and HR were also measured at the 1st and 6th minutes post-test in the sitting position. Two tests were performed with a 30-min interval, and the average 6MWD$_M$ value was used (Dolmage et al., 2011). Post-test hemodynamic variables used for the analyses corresponded to the 'best effort' test. The maximal HR was predicted using a prediction model (Tanaka et al., 2001).

2.6. Prediction model of functional capacity (indirect method)

The following risk factors for hypertension entered the model as they also comprise predictors of 6MWD$_M$ in the healthy population: age, body mass, body height, and sex ('male' = 1; 'female' = 0). MBP, a disease-specific independent predictor of the 6MWD$_M$ also entered the model. IPAQ, an indirect estimate of physical activity, entered the model as an ordinal variable: 'not active' = 1; 'irregularly active B' = 2; 'irregularly active A' = 3; 'active' = 4; 'very active' = 5. Irregularly active subjects were categorized as type A and B; type A implies a subject matched at least one criterion regarding the recommended frequency (5 days/week) or duration of physical activity (150 min/week), whereas type B implies a subject does not match either criterion.[1] All variables entered the model in a forward stepwise

[1] https://edisciplinas.usp.br/pluginfile.php/3343547/mod_resource/content/1/IPAQ.pdf.

Table 3
Multivariate linear regression analysis for prediction of the 6-min walked distance in patients with hypertension.

Model term	β coefficient [95%CI]	Standard error	*t* value	*p value*
Intercept	611.347 [136.010; 1086.684]	238.271	2.566	0.012
MBP (mmHg)	−4.446 [-6.091; −2.801]	0.825	−5.391	<0.001
IPAQ (=0)	−129.559 [-193.818; −65.299]	32.211	−4.022	<0.001
IPAQ (=1)	−120.460 [-182.556; −58.363]	31.127	−3.870	<0.001
IPAQ (=2)	0.000	–	–	–
Sex (=0)	−73.356 [-113.348; −33.365]	20.046	−3.659	<0.001
Sex (=1)	0.000	–	–	–
Age (years)	−1.511 [-2.523; −0.499]	0.507	−2.979	0.004
Height (m)	267.630 [10.749; 524.511]	128.766	2.078	0.041

method using the *F*-test value as a criterion for entry ($p < 0.05$) and removal ($p < 0.10$) of variables.

2.7. Estimating target-values for the $6MWD_P$

Target-values can be predicted using the actual data from the patient and the model developed herein under scenarios related to two major therapeutic aims in hypertension. A first scenario comprised reducing both systolic and diastolic blood pressure values in $6MWD_P$, accomplished by inputting borderline optimal blood pressure values (i.e. 119/79 mmHg) that yield a MBP equal to 92.3 mmHg (=79+[119−79]/3). A second scenario comprises changing modifiable risk factors that reduce total cardiovascular risk in $6MWD_P$, accomplished by inputting an 'active' classification with IPAQ = 4. Finally, both optimal conditions of blood pressure and physical activity can be used to assess their combined effect in $6MWD_P$. Other personal characteristics are assumed as either non-modifiable risk factors or stable between short-time retests.

2.8. Statistical analysis

A complete-case analysis was conducted using SPSS 22 (IBM Inc., Armonk, NY, USA) because no missing data occurred. Statistical significance was considered at $p < 0.05$ (two-tailed). Reporting of statistical data followed Statistical Analyses and Methods in the Published Literature' Guidelines (Lang and Altman, 2015).

Descriptive results are shown as mean ± SD [minimum; maximum] and frequency (%). Outliers were investigated using the Cook's D statistics. Overall performance measures of the regression consisted of adjusted R^2 value and bias ($6MWD_M$ − $6MWD_P$). As the first step towards checking the modeling assumptions and identifying predictors of $6MWD_M$ a regression's diagnosis was performed using Pearson's correlation coefficient between dependent and independent variables, as well as among independent ones (Collins et al., 2014); multicollinearity was also assessed using the variance inflation factor. To further explore the assumptions of the linear regression an analysis of residuals was performed using histograms and the one-sample Kolmogorov-Smirnov test with the Lilliefors correction to test the null hypothesis of Normality of distribution of residues. The accuracy of the model's prediction was verified using the calibration plot – $6MWD_M$ *vs.* $6MWD_P$, along with regression lines showing slope and intercept – and limits of agreement (LOA) plot. The LOA plot was used to determine bias and agreement between $6MWD_M$ and $6MWD_P$, and the error was determined as the SD of the bias (Bland and Altman, 2010). LOA were defined as upper and lower $CI_{95\%}$ and were determined by the mean difference ±1.96SD. The bias was tested against zero with the one-sample Student's *t*-test.

3. Results

3.1. Test performance

Participants completed the 6MWT without interruption (Table 2). Lower $6MWD_M$ values were observed for the second test compared with the first one (334 ± 103 m *vs.* 316 ± 106 m, $p = 0.001$). Averaging both tests, the patients walked 325 ± 101 m. Hemodynamic variables exhibited significantly high values (all $p < 0.001$) during the first minute after the test and remained significantly high during the sixth minute despite a trend of reduction to pre-test values. No outlier of $6MWD_M$ was detected (highest Cook's D = 0.183, participant #5).

3.2. Regression diagnosis

Correlation analysis of $6MWD_M$ and its potential predictors showed that the $6MWD_M$ was positively correlated to sex (0.647, $p < 0.001$), IPAQ level (0.507, $p < 0.001$), body height (0.478, $p < 0.001$), and body mass (0.252, $p = 0.028$), but negatively correlated to MBP (−0.458, $p < 0.001$) and age (−0.375, $p = 0.001$). Correlation analysis among potential predictors was statistically significant for the paired analysis of: sex and height (0.697, $p < 0.001$), mass (0.330, $p = 0.004$), and IPAQ (0.283; $p = 0.013$); age and IPAQ (−0.243, $p = 0.034$); body mass and height (0.460, $p < 0.001$); and MBP and IPAQ (−0.312, $p = 0.006$). The assumption of the model regarding multicollinearity was met since the variance inflation factor was low for all included predictors: MBP (1.113), IPAQ (1.233), age (1.155), sex (2.270), and body height (2.077).

3.3. The prediction model and its overall performance

The overall performance of the model was significantly improved with the forward stepwise inclusion of sex, MBP, IPAQ, age and body height (adjusted R^2 values: 0.410, 0.573, 0.641, 0.665, and 0.680, respectively; all $p < 0.05$). Body weight was automatically removed from the model and the final multivariate linear prediction model for the $6MWD_M$ is exhibited in equation (1):

$$6MWD_P = 611.347 – 4.446 \times MBP + 267.630 \times height - 1.511 \times age + IPAQ_{code} + sex_{code}, \quad (1)$$

where IPAQ(2) = −129.559, IPAQ(3,4) = −120.460, or IPAQ(5) = 0.000; and sex(female) = −73.356 or sex(male) = 0.000 and a SE of bias equal to 6.3 m.

Table 3 shows the results of the multivariate model with all the retaining variables simultaneously. All variables retained in the model are correlated to the $6MWD_M$ and also independent predictors of the $6MWD_M$. The $6MWD_P$ estimated with equation (1) using values from patients yielded a group-average value of 325 ± 87 m, being 46 (61%) patients below this point.

3.4. Model's calibration

Statistical assumptions regarding the regression model were not violated as Fig. 2 shows no obvious relation between the bias and the mean, no apparent skew and a Gaussian distribution of residues was not rejected ($p = 0.200$). For the 6MWT data, the bias [$CI_{95\%}$] was −0.7 [-13; 12] m with a SD of ±54.9 m. Lower and upper LOA and respective $CI_{95\%}$ are −108 m [-130; 87] and 107 m [85; 129]. Only 4 (5%) participants were situated outside the LOA.

3.5. Target-values predicted using optimal values

The effects of the scenarios on the $6MWD_P$ varied from almost none to considerable depending on the therapeutic aims considered and whether both were inputted as single or combined targets. Inputting borderline optimal blood pressure values the $6MWD_P$ resulted in a target-value of 323 ± 75 m with 45 (59%) patients below this target; this value represents less than −1% from the $6MWD_P$ inputting actual MBP in equation (1). Inputting a healthy lifestyle change in physical activity the $6MWD_P$ resulted in 423 ± 72 m with 63 (83%) patients below this target; this represents an average increment of 23% in the $6MWD_P$. Under both therapeutic aims, the $6MWD_P$ resulted in a target-value of 420 ± 60 m, again with 63 (83%) patients below this target-value and 23% increment on average.

4. Discussion

We found that men, higher body height, and lower age are associated with a higher $6MWD_M$ and were retained in the model as expected because they comprise data already known to be associated with the $6MWD_M$ in health (Casanova et al., 2011) and hypertension (Ramos et al., 2014). The retention of MBP in the model was also expected due to its known inverse association with functional outcomes in general and particularly the $6MWD_M$ as reported in previous studies (Hajjar et al., 2007; Ramos et al., 2014). Nonetheless, the retention of lifestyle data – i.e. higher physical activity as assessed by IPAQ is associated to higher $6MWD_M$ – was a major novelty and interesting result for this population.

A sedentary lifestyle is a well-known risk factor for several cardiovascular diseases including hypertension; in a vicious cycle, cardiovascular diseases might yield impairments in functional capacity thus favoring a more sedentary lifestyle (Hajjar et al., 2007; Ramos et al., 2014). IPAQ is a tool for determination of physical

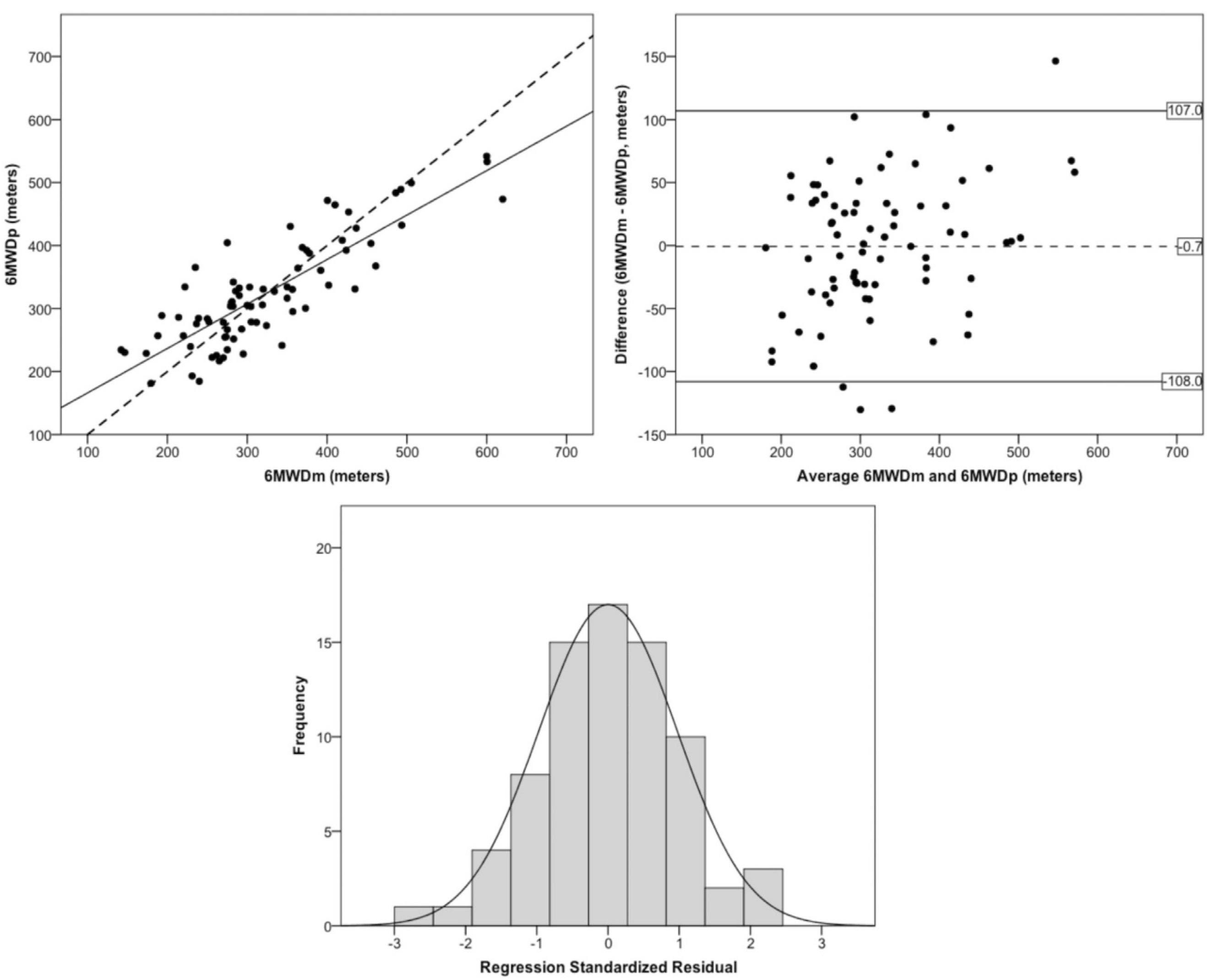

Fig. 2. Statistical assessment of the multivariate model. *Top-left*: Calibration plot of the measured versus predicted 6-min walked distance. *Top-right*: Limits of agreement plot of the averaged values and bias. *Bottom*: Histogram of residues of the model for prediction of the 6-min walked distance.

activity at the population level (Matsudo et al., 2012), but because of this cross-sectional design, it is not possible to differentiate whether patients presented low IPAQ scores as a risk factor or outcome of the underlying morbid process. However, being a modifiable risk factor that might be addressed in cardiac rehabilitation programs, the retention of physical activity on the final model highlights the need for adopting healthier lifestyles including regular physical activity for reducing the total cardiovascular risk in patients with hypertension.

The overall performance of the model revealed that it overrides the best prediction model of $6MWD_M$ obtained from healthy participants in a Brazilian study (Iwama et al., 2009) and other populations in rehabilitation science (Canning et al., 2006; Deuschle et al., 2011; Falvo and Earhart, 2009a, 2009b) as judged by the adjusted determination coefficient, which was higher herein. Our model also outperformed the model obtained for $6MWD_M$ in adults with Parkinson's disease with respect to accuracy and precision (bias ± SD) (Falvo and Earhart, 2009a). This strongly suggests that our model captured the disease-specific impairment in functional capacity in patients with hypertension. Data from model's calibration show that general assumptions regarding linear regression modeling were not violated, providing further confidence in our results. Despite the observed small SD of bias in our study, Fig. 2 illustrates the variability in 6MWD in those patients with hypertension and the LOA reflected the variety of phenotypes in hypertension.

The ranges of values for all predictors in our study are representative of the population with hypertension, which is required for clinical purposes and increased our confidence in the external validity of the model. Prediction outside this range of the data relies heavily on the regression assumptions, and confidence bands widen as predictions are made away from the mean (Toutenburg and Shalabh, 2009). Nonetheless, our sample consists of patients up to hypertension stage-II and thus the generalization of these results to those with more advanced stages of hypertension must be made with caution. The 'case-to-case' approach yields a model that incorporates the covariance among independent variables. Therefore, we did not compare our estimates of $6MWD_P$ using equations obtained from healthy populations because it would compromise the new model's validity.

The theoretical scenarios for the prediction of target-values unveil an interesting debate. Currently, the expected increment in $6MWD_M$ during cardiac rehabilitation programs is not yet clearly defined for patients with hypertension. The prediction of 6MWD under the most optimal scenario of major therapeutic aims suggests that patients need to increment on average 23% from their baseline $6MWD_M$ to match the performance of subjects from the same population with optimal MBP and IPAQ. For comparison, an average increase of 12%–40% in the $6MWD_M$ was reported for patients with chronic heart failure under various interventions (Papathanasiou et al., 2013); percentage of increment following cardiac rehabilitation was reported (Salbach et al., 2015) in range the 10%–28%. Notice that the 23% increment is four-fold the increment between test-retest (approximately −5%). Our proposed increment in averaged $6MWD_M$ is thus plausible and requires further investigation.

Predictive modeling is the process of applying a statistical model to data for the purpose of predicting new observations based on available information (Shmueli, 2010). Because the 6MWD is known to vary according to personal characteristics the American Thoracic Society (Crapo et al., 2002) recommended the interpretation of the 6MWT accordingly, which is a complex task due to the multivariate nature of the known influential factors. Therefore, prediction equations of the 6MWD are advantageous at least under the following reasoning. On the one hand, prediction models developed in country-specific health populations (Dourado et al., 2011; Salbach et al., 2015) can be used to determine reference values considering the multiple factors simultaneously. On the other hand, population-specific prediction models capture the disease-related unique aspects influencing functional capacity (Canning et al., 2006; Deuschle et al., 2011; Falvo and Earhart, 2009a, 2009b). Both developing strategies should be interpreted as complementary rather than opposed because they clearly provide distinct information. A key point is that prediction models should be considered as companion methods rather than replacements for the direct measurement, provided the direct method is readily available in the clinical setting and has acceptable clinimetric properties − as is the case for the 6MWT (Bellet et al., 2012; Papathanasiou et al., 2013).

Our findings must be interpreted in light of this study's limitations. First, it is worth noticing that in this cross-sectional study it is not possible to determine the cause-effect relationship between dependent and independent variables. Second, we aimed at keeping the prediction model as simple as possible to allow a likewise quick prediction in the clinical setting, but it is apparent that other latent predictors that we did not measure might be influential. Including other risk factors such as surrogate measures of vascular remodeling (Ferreira et al., 2012) would preclude using the current model in large samples as they require dedicated equipment and training. Third, as recommended by current evidence (Collins et al., 2014), the model developed herein warrants external validation in samples that were not used to develop the model to eval how optimistic was the internal validation. Nonetheless, the current model encourages future research on other cardiovascular risk factors as potential predictors of the 6MWD.

Our study presents major strengths as compared to previous studies. Firstly, our sample was the largest one to perform the 6MWT under the same protocol unlike previous studies (Ramos and Ferreira, 2014) and matched other studies (Canning et al., 2006; Deuschle et al., 2011; Falvo and Earhart, 2009a, 2009b) under the patient-patient paradigm in rehabilitation. Secondly, we used advanced statistical methods for development of the prediction model that were not fully applied in Brazilian studies for developing prediction models (Toutenburg and Shalabh, 2009). Thirdly, the model's input comprises variables that are easily obtained in the clinical setting and that have been systematically observed as significantly correlated to the $6MWD_M$. Finally, by adhering to international guidelines for reporting the development of multivariate regression models (Collins et al., 2015) and statistical analysis (Lang and Altman, 2015) we expected to improve the clinical application of our model and to contribute to future systematic reviews on this subject.

Perspectives on the rehabilitation science are promising. Randomized clinical trials have been proposed for patients with hypertension using the 6MWD as a surrogate measure of functional capacity (Buford et al., 2015). Future research must focus on the predictive performance of our model in external datasets, the discrimination analysis of our model, as well as the validity of the model for predicting target values (Collins et al., 2014).

5. Conclusions

Sex (men), higher body height, higher physical activity, lower mean blood pressure, and lower age are correlated with higher $6MWD_M$ in patients with hypertension, being all multivariate predictors of functional capacity in this population. Target-values can be proposed for therapeutic aims related to hemodynamics and lifestyle.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jbmt.2018.01.010.

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