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ORIGINAL ARTICLE

The six-minute walk distance is a marker of hemodynamic-related functional capacity in hypertension: a case–control study

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This study investigated the association between hemodynamic variables and the 6-minute walk distance (6MWD) in adults with and without hypertension and explored the role of hemodynamic variables as predictors of 6MWD. Patients undergoing antihypertensive medication therapy ($n=41$) and sex-matched healthy subjects ($n=41$) were evaluated for their clinical status and cardiovascular risk factors. Two 6-minute walk tests were performed along an 18-m corridor with a 30-minute rest interval. The intraclass correlation (ICC) was high among patients (ICC = 0.984 (0.965; 0.992), $P<0.001$) and controls (ICC = 0.987 (0.832; 0.996), $P<0.001$). The patients presented 6MWD values that were significantly lower than those of healthy controls (338.8 ± 112.8 *vs.* 388.0 ± 66.7 m, $P=0.010$). In patients, the 6MWD was significantly and positively correlated with sex (0.737; $P<0.001$), height (0.502; $P<0.001$) and weight (0.303; $P=0.027$). In addition, negative and significant correlations were observed between 6MWD and the mean (−0.577; $P<0.001$), systolic (−0.521; $P<0.001$), diastolic (−0.505; $P=0.001$) and pulse (−0.353; $P=0.015$) pressures after simultaneous adjustment for age, body height and weight. The same behavior was observed in healthy controls (except for pulse pressure), albeit with lower correlation values. A regression model with sex, age, height and weight explained 52.2% ($P<0.001$) of the variance. The highest explained variance in patients (64.8%; $P<0.001$) and controls (56.5%; $P<0.001$) was observed after replacing the body weight with mean pressure in the model. The 6MWD is inversely associated with hemodynamic variables in both groups and is lower in patients with hypertension compared with healthy controls. Hemodynamic variables, particularly the mean pressure, should be included in prediction equations for 6MWD.

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Keywords: functional capacity; rehabilitation; high blood pressure

INTRODUCTION

Hypertension is the leading risk factor for cardiovascular diseases (CVDs) and a major public health problem worldwide[1] and in Brazil. Despite a 6% reduction over the past three decades,[2] the prevalence of hypertension in Brazil is still nearly 30%. The cardiovascular risk for adverse outcomes increases continuously with blood pressure values that exceed optimum levels.[3,4] Hypertension is related to structural and functional changes in small-, middle- and large-sized arteries that may progress to damage of target organs, such as the heart, brain and kidneys.[5] Microvascular arterial remodeling also occurs in the skeletal muscles of untreated adults with hypertension.[6] Such damage compromises the functional capacity and long-term independence in activities of daily living, such that patients with hypertension are at high risk of developing physical disabilities.[7] Because cardiac rehabilitation aims to interrupt the mutual reinforcement between high blood pressure and its underlying mechanisms, the early recognition of functional impairments in patients with hypertension may allow for immediate intervention to prevent more severe disabilities.

As its first use in patients undergoing cardiac rehabilitation,[8] the six-minute walk test (6MWT) has been considered as a valid and reliable method in the assessment of functional capacity in outpatients.[9–11] The 6MWT evolved from other timed walk tests[12,13] and is preferred to other methods for the assessment of functional capacity because it is safe, well tolerated by patients, easy to perform, inexpensive and similar to daily-living activities.[14] This test's main outcome—the six-minute walk distance (6MWD)—is analyzed either as an absolute or percent value based on reference equations obtained from healthy subjects. Despite the number of published equations for the adult population,[15] the use of equations from national samples is advocated as 6MWT results have been demonstrated to be region-dependent.[16]

Literature on the 6MWT in patients with hypertension is limited. Clinical trials have reported low absolute values of the 6MWD in

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adults with grade-I or -II hypertension and comorbidities, which improved after physical rehabilitation programs.[17–19] Cross-sectional studies have suggested diminished 6MWD in women with grade-I hypertension with comorbidities,[20] whereas another cross-sectional study[21] demonstrated preserved 6MWD in men with grade-I hypertension without comorbidities along with a significant 8% overestimation of the predicted distance using a foreign equation.[22] The 6MWD is correlated with other functional outcomes such as the 'Timed Up and Go' test in women with hypertension and comorbidities.[23] However, these observations were derived from small samples with specific characteristics and thus were subject to spectrum bias, resulting in limited external validity.[24]

The goodness-of-fit (R^2) of Brazilian prediction equations[25–27] based on personal variables (age, sex, body height and weight) ranges from 30 to 60%. Such low values suggest that other important variables should be considered as predictors of 6MWD. Because some factors associated with the 6MWD in healthy subjects are also risk factors for CVD—that is, sex, age, weight and height[28–31]—it is hypothesized that other factors related to the pathophysiology of hypertension may contribute to a better prediction of the 6MWD in this population. Notably, the association between 6MWD and hemodynamic variables in adults with and without hypertension remains unknown, as well as their potential role as predictors of 6MWD. Therefore, the aims of this study are twofold: (1) to test the association between hemodynamic variables and the 6MWD in adults with hypertension; and (2) to explore the role of hemodynamic variables as predictors of the 6MWD to be included in a population-specific equation.

METHODS

Ethics

The Institutional Ethics Committee approved this study protocol before execution (CAAE 05517012.8.0000.5235). All subjects signed an informed consent form after being informed of the study aims and procedures.

Study design and sample size

This was a sex-matched, case–control study. The examiner was not blinded to the participants' group as the 6MWD outcome is not likely to be influenced by this information. Considering the association between the 6MWD and hemodynamic variables as the main outcome of this study, a minimal sample size of 36 participants per group was necessary to observe a minimal correlation of 0.41 (weak or higher) at a 5% significance level and 80% study power.

Participants

Table 1 summarizes the sample group's descriptive data. Forty-one patients undergoing routine antihypertensive medication therapy were consecutively assessed for eligibility from December 2012 to June 2013 at the Division of Arterial Hypertension of the National Institute of Cardiology (RJ, Brazil). Forty-one healthy subjects were also assessed for eligibility among the patient's relatives and individuals who accompanied the patients during the clinical visits (Figure 1). Eligibility was considered depending on the following inclusion criteria: age >18 years; no physical limitations that influence walking; and no recent history (<6 months) of musculoskeletal pain in the lower limbs and spine. The following additional criteria were applied for patients: an established diagnosis of primary systemic arterial hypertension before the study (systolic pressure (SP) ⩾140 mm Hg and/or diastolic pressure (DP) ⩾90 mm Hg on repeat visits);[5] completion of biochemical blood analysis; and the absence of valvular disease, ventricular dysfunction and cardiac arrhythmias.

History, physical examination and laboratory analysis

The patient's clinical histories were obtained and they underwent anamnesis and physical examination for the assessment of their personal characteristics

Table 1 Sample characteristics

	Groups		
Variable	*Hypertension* (n = 41)	*Healthy* (n = 41)	P-*value* (*between groups*)
Men, *n* (%)	18 (44%)	19 (46%)	0.824[a]
Age (years)	48.9 ± 11.6	32.8 ± 6.2	<0.001[b]
Height (m)	1.71 ± 0.07	1.72 ± 0.07	0.344[b]
Weight (kg)	83.2 ± 15.2	76.2 ± 9.1	0.007[b]
Body mass index (kg m^{-2})	28.2 ± 4.2	25.7 ± 2.0	0.001[b]
Hypertension course (months)	63.9 ± 72.6	0 ± 0	NT
Office blood pressure (mm Hg)			
Systolic	156.4 ± 17.7	130.0 ± 6.0	<0.001[b]
Diastolic	91.3 ± 8.0	84.7 ± 4.5	<0.001[b]
Mean arterial pressure	113.0 ± 10.0	99.8 ± 4.5	<0.001[b]
Pulse pressure	65.0 ± 14.5	45.3 ± 4.5	<0.001[b]
Risk factors, n *(%)*			
Quantity of risk factors	0 (0; 2)	2 (0; 5)	NT
Smoker	15 (37%)	6 (15%)	0.023[a]
Sedentary	26 (63%)	8 (20%)	<0.001[a]
History of premature CVD	15 (37%)	0 (0%)	NT
Obesity	11 (27%)	1 (2%)	0.002[a]
Dyslipidemia	35 (85%)	*	NT
Diabetes mellitus	10 (24%)	*	NT
Physical activity level			
Very active	2 (5%)	10 (24%)	0.001[a]
Active	12 (29%)	23 (56%)	<0.001[a]
Irregularly active A	9 (22%)	4 (10%)	0.002[a]
Irregularly active B	18 (44%)	4 (10%)	<0.001[a]
Antihypertensive drug treatment, n *(%)*			
Quantity of medications	3 (1; 5)	0 (0; 0)	NT
Diuretics	40 (98%)	0 (0%)	NT
Vasodilator	39 (95%)	0 (0%)	NT
β-Blocker	18 (44%)	0 (0%)	NT
ACE inhibitors	8 (20%)	0 (0%)	NT
Sympatholytic	3 (7%)	0 (0%)	NT
AT2 antagonist	1 (2%)	0 (0%)	NT

Abbreviations: ACE, angiotensin-converting enzyme; CVD, cardiovascular disease; irregularly active A, present one criterion for physical activity regarding frequency or duration; irregularly active B, does not match both criteria of frequency nor duration for physical activity; NT, variables not tested owing to cells with zeroed values or data not available.
[a]Categorical variables compared between groups by the *Z*-test.
[b]Continuous variables compared between groups by the *t*-test.
*Exam not performed.

after a 10-minute rest in the sitting position. The same examiner performed all of the assessments in a temperature-controlled room (21–23 °C) during the morning (0800—1100 h) and in the presence of a physician.

Information about the self-reported duration of hypertension, smoking habits, history of premature CVD (men <55 years, women <65 years)[5] and physical activity level[32,33] were collected. Body height and weight were obtained using an analog scale and rounded to the closest decimal value; these values were used to calculate the Quetelet's body mass index. The heart rate (HR), SP and DP were measured in the office using an oscillometric-automated device positioned at the right-sided wrist (model BP3AF1-3; Onbo Electronic, Bao An Shin, Shenzen, China). The participant was allowed to rest for 5–10 min in a seated position before three repeat blood pressure measurements were obtained, spaced by a 1–2 min interval.[5] Both SP and DP were used to calculate the pulse pressure (PP = SP − DP) and mean

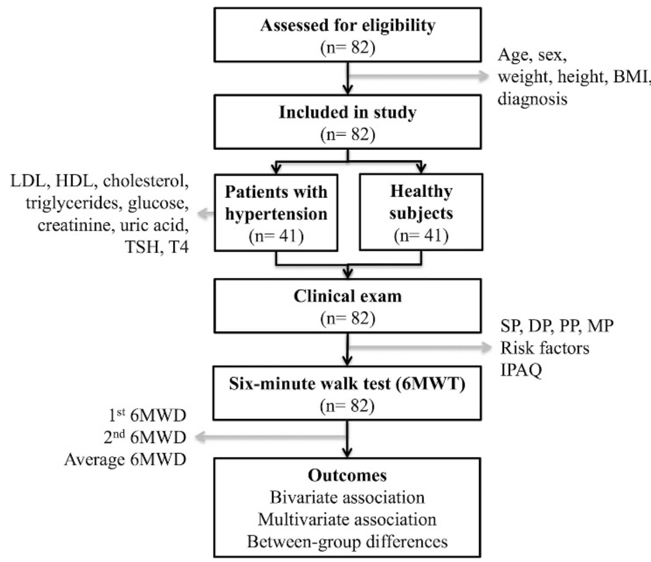

Figure 1 Study flowchart.

arterial pressure (MP = DP + PP/3). All arterial pressure measurements were reported as the average of the three measurements. Laboratory biochemical analyses for the assessment of cardiovascular risk factors were performed in the fasting state and included serum creatinine, serum glucose, uric acid, total triglycerides, total cholesterol, low-density lipoprotein, high-density lipoprotein and C-reactive protein (CRP).

The hypertension grade was determined according to the average of the office blood pressure values obtained during screening.[5] The additional cardiovascular risk factors that were assessed included: obesity (body mass index $\geqslant 30\,\mathrm{kg\,m^{-2}}$);[34] sedentary lifestyle (IQPA: sedentary or irregularly active during the prior month); dyslipidemia (low-density lipoprotein-cholesterol $<100\,\mathrm{mg\,dl^{-1}}$ for controls or $<70\,\mathrm{mg\,dl^{-1}}$ for cases, high-density lipoprotein-cholesterol $>50\,\mathrm{mg\,dl^{-1}}$ and triglycerides $>150\,\mathrm{mg\,dl^{-1}}$, according to the American Diabetes Association, 2013); and diabetes mellitus (fasting serum glucose $>126\,\mathrm{mg\,dl^{-1}}$).

Functional capacity: the 6MWT

The 6MWT was performed according to the general published recommendations,[35] with minor adaptations.[21] Before the 6MWT, subjects were requested to not engage in physical activities for 24 h and to not smoke or ingest alcohol for at least 3 h. All 6MWT were performed outdoors along an 18-m corridor delimited with cones at both ends.

All subjects were instructed to walk as fast as they could along the corridor. They were also informed to slow down their walk or to interrupt it if necessary. During all tests, the participants were monitored verbally by the Borg modified scale every 2 min. For the duration of the test, the examiner did not use incentive phrases, although the participants were informed about the test duration 3 min after its start ('Three minutes left!'). By the sixth minute, each subject was requested to stop and the number of runs and the remaining distance of the last run were summed. The blood pressure and HR were measured before the test, and during the first and sixth minute after finishing the test in the sitting position. Two tests were performed with a 30-minute interval, and the average of the two 6MWD values was used to best approximate a representative true value.[36] The post-test hemodynamic variables used for the analyses corresponded to the 'best effort' 6MWT.

The 6MWD absolute values were provided with their percent values predicted using three equations derived from Brazilian samples.[25–27] The maximal HR was predicted using a regression equation for adults.[37]

Statistical analysis

Continuous and ordinal variables were described as the mean ± s.d. or median (minimum; maximum), whereas nominal variables were represented by *n* (%). Normality of distributions was evaluated using the Kolmogorov–Smirnov test. Continuous variables were compared between and within groups by the one-tailed Student's *t*-test and paired *t*-test, respectively. Categorical variables between groups were compared by the *Z*-test and were coded as dummy variables: sex (male = 1, female = 0) and risk factors for CVD (present = 1; absent = 0). The repeatability of the 6MWT was measured by the two-way random intraclass coefficient (ICC and 95% confidence interval) with absolute agreement. The hemodynamic variables that were evaluated pre- and post-6MWT (first and sixth minute) were compared through one-way analysis of variance (ANOVA) with Dunnett's *post hoc* test (control: pre-6MWD). Bivariate associations were examined by one-tailed Pearson's *r* correlation coefficient between 6MWD and hemodynamic variables. Partial correlations for hemodynamic variables were also estimated after controlling for possible confounding variables (age, height and weight). Several linear regression models were generated to explore the role of hemodynamic variables as predictors of absolute 6MWD. Each model was limited to four dependent variables because of the sample size (minimal ratio case: variable = 10:1). A 'reference' model (no. 0) was created with variables most commonly used in 6MWD prediction equations (sex, age, height and weight).[15] Four other models were generated with three fixed variables (sex, age and height) because of significant high correlations with the 6MWD plus a hemodynamic variable: SP, DP, MP or PP (nos. 1 to 4, respectively). The adjusted R^2 and *P*-values were calculated to evaluate each model fit. Statistical significance was considered as $P<0.05$ with a 95% confidence interval. Analyses were conducted using SPSS 17 (SPSS, Chicago, IL, USA).

RESULTS

Performance and repeatability of 6MWT

All participants completed the 6MWT without interruption. The intraclass correlation was high among patients (ICC = 0.984 (0.965; 0.992), $P<0.001$) and controls (ICC = 0.987 (0.832; 0.996), $P<0.001$).

Significantly lower 6MWD values were observed for the second test compared with the first in both groups of patients (344.6 ± 112.2 *vs.* 331.1 ± 115.0 m, $P = 0.005$) and healthy controls (387.7 ± 66.8 *vs.* 376.1 ± 68.4 m, $P<0.001$), with greater variability in the former group (Table 2). The 6MWD was significantly lower in patients compared with healthy controls for the first and second tests ($P = 0.019$ and 0.022, respectively). Patients presented an average 6MWD that was significantly lower than that of healthy controls (338.8 ± 112.8 *vs.* 388.0 ± 66.7 m, $P = 0.010$).

All Brazilian equations overestimated the 6MWD (Table 2). Iwama's equation yielded significantly lower predicted values for patients compared with healthy controls (59.9 ± 16.6% *vs.* 65.5 ± 9.0%, $P = 0.032$), whereas no significant differences were observed for the 6MWD percent values, as predicted by the equations of Dourado *et al.*[15] (53.2 ± 15.2% *vs.* 55.7 ± 7.4%, $P = 0.177$) or Soares and Pereira[27] (58.7 ± 18.3% *vs.* 61.6 ± 9.4%, $P = 0.184$).

The hemodynamic variables SP, DP and HR exhibited significantly (all $P<0.001$) high values in both groups during the first minute after the test, and remained significantly high during the sixth minute despite a trend of reduction to pre-6MWT values (Table 2).

Association between 6MWD and other variables

In patients, the 6MWD was significantly and positively correlated with sex (0.737; $P<0.001$), height (0.502; $P<0.001$) and weight (0.303; $P = 0.027$) (Table 3). Negative and significant correlations were observed between 6MWD and HR (−0.604; $P<0.001$), MP (−0.518; $P<0.001$), SP (−0.480; $P = 0.001$), DP (−0.441; $P = 0.002$), age (−0.383; $P = 0.007$), duration of hypertension (−0.361; $P = 0.010$) and PP (−0.341; $P = 0.015$). The simultaneous adjustment for age, height and weight yielded, nevertheless, significant and stronger correlations between all hemodynamic variables

Table 2 Outcomes of the six-minute walk test

Variables	Groups: Hypertension (n = 41)	Healthy (n = 41)	P-value (between groups)
Six-minute walk distance (m)			
Test no. 1	344.6 ± 112.2	387.7 ± 66.8	0.019[a]
Test no. 2	331.1 ± 115.0	376.1 ± 68.4	0.022[a]
Test nos. 2 − 1 (%)	−3.8 ± 7.4	−3.1 ± 2.9	NT
P-value (within group)	0.005[b]	< 0.001[b]	
Averaged 6MWD	338.8 ± 112.8	388.0 ± 66.7	0.010[a]
Predicted values of 6MWD (%)			
The Iwana's equation	59.9 ± 16.6	65.5 ± 9.0	0.032[a]
The Dourado's equation	53.2 ± 15.2	55.7 ± 7.4	0.177[a]
The Soares and Pereira's equation	58.7 ± 18.3	61.6 ± 9.4	0.184[a]
Systolic blood pressure (mm Hg)			
Rest	156.4 ± 17.7	130.0 ± 6.0	NT
First minute	174.6 ± 18.1[c]	155.5 ± 8.5[c]	NT
Sixth minute	165.6 ± 16.6[c]	135.3 ± 5.9[c]	NT
P-value (within group)	< 0.001[d]	< 0.001[d]	
Diastolic blood pressure (mm Hg)			
Rest	91.3 ± 8.0	84.7 ± 4.5	NT
First minute	103.5 ± 10.1[c]	100.6 ± 6.3[c]	NT
Sixth minute	95.2 ± 7.2[c]	89.7 ± 4.6[c]	NT
P-value (within group)	< 0.001[d]	< 0.001[d]	
Heart rate (beats min^{-1}) (%)			
Rest	90.0 ± 6.1 (52 ± 5)	86.7 ± 4.1 (47 ± 3)	NT
First minute	109.1 ± 13.7 (63 ± 9)[c]	107.6 ± 9.9 (58 ± 6)[c]	NT
Sixth minute	97.5 ± 9.6 (56 ± 6)[c]	91.9 ± 4 (50 ± 3)[c]	NT
P-value (within group)	< 0.001[d]	< 0.001[d]	

Abbreviations: 6MWD, six-minute walk distance; NT, variables not tested owing to cells with zeroed values or data not available.
[a]Continuous variables compared between groups by the *t*-test.
[b]Continuous variables compared within groups by the paired *t*-test.
[c]Significantly higher than 'Rest'.
[d]Continuous variables compared within group by the one-way analysis of variance.

and the 6MWD, except for HR, which presented a weaker yet significant correlation.

In healthy controls, the 6MWD was also significantly and positively correlated with sex (0.680; $P<0.001$), height (0.635; $P<0.001$) and weight (0.398; $P=0.005$). By contrast, the averaged 6MWD was negatively correlated to MP (−0.304; $P<0.027$), SP (−0.290; $P=0.033$) and DP (−0.269; $P=0.044$), but not to HR (−0.231; $P=0.073$), age (−0.147; $P=0.180$) or PP (−0.120; $P=0.227$). The simultaneous adjustment for age, height and weight yielded significant and stronger negative correlations between all hemodynamic variables and the 6MWD again, except for PP.

Prediction of the 6MWD using clinical and hemodynamic variables

The average 6MWD was significantly predicted by all models (nos. 0–4) (all $P<0.001$) in both groups (Table 4). In patients with hypertension, model no. 0 exhibited the lowest explained variance (52.2%). Replacing the body weight by PP, SP, DP or MP yielded progressively higher explained variances of 54.8%, 61.1%, 62.6% and 64.8%, respectively. Healthy controls exhibited a similar explained variance of model no. 0 (54.7%) compared with the patients with hypertension. Likewise, replacing the body weight by PP, SP, DP or MP yielded progressively higher explained variances of 51.2%, 54.8%, 56.1% and 56.5%, respectively.

DISCUSSION

This study investigated the association between hemodynamic variables and the 6MWD in adults with and without hypertension, and explored the role of hemodynamic variables as predictors of the 6MWD for inclusion in a population-specific equation. The main outcomes of this study are: (1) the 6MWD is inversely associated to MP, SP, DP and PP both in patients with hypertension and in healthy controls; and (2) hemodynamic variables, mainly MP, improve the prediction of the 6MWD in both groups. This is the first study to explore the differences in the 6MWT between patients with hypertension and healthy subjects, as well as to confirm that hemodynamic variables can be used for the prediction of functional capacity.

The high repeatability between two tests in this study was an expected outcome as this has been previously reported for patients undergoing cardiac rehabilitation (ICC = 0.96 (0.93; 0.98))[38] and healthy subjects (ICC = 0.84 for three 6MWT).[39] However, a 3–4% reduction in the 6MWD in the second test was unanticipated because the second 6MWD usually increases by 3–5% in patients with CVD[38] and in healthy subjects,[39] allegedly due to the 'learning effect'.

Table 3 Bivariate correlation coefficients between the averaged six-minute walk distance and other variables

Variables	Adjusted for confounders	Groups	
		Hypertension (n = *41)*	*Healthy* (n = *41)*
Sex[a]	None	0.737; $P<0.001$	0.680; $P<0.001$
Height	None	0.502; $P<0.001$	0.635; $P<0.001$
Weight	None	0.303; $P=0.027$	0.398; $P=0.005$
Age	None	−0.383; $P=0.007$	−0.147; $P=0.180$
Duration of hypertension	None	−0.361; $P=0.010$	NT
Heart rate	None	−0.604; $P<0.001$	−0.231; $P=0.073$
	Adjusted	−0.489; $P=0.001$	−0.328; $P=0.022$
Pulse pressure	None	−0.341; $P=0.015$	−0.120; $P=0.227$
	Adjusted	−0.353; $P=0.015$	−0.015; $P=0.464$
Diastolic pressure	None	−0.441; $P=0.002$	−0.269; $P=0.044$
	Adjusted	−0.505; $P=0.001$	−0.374; $P=0.010$
Systolic pressure	None	−0.480; $P=0.001$	−0.290; $P=0.033$
	Adjusted	−0.521; $P<0.001$	−0.329; $P=0.022$
Mean pressure	None	−0.518; $P<0.001$	−0.304; $P=0.027$
	Adjusted	−0.577; $P<0.001$	−0.391; $P=0.008$

Adjusted, partial correlation coefficient controlled for age, height and weight; NT, variables not tested owing to cells with zeroed values or data not available.
Pearson's *r* correlation coefficient.
[a]Categorized as a dichotomous variable (male = 1).

Although a reduction of the 6MWD in sequential tests may suggest a low-effort test, this explanation is unlikely because the post-6MWT predicted an HR increase similar to other studies.[25,27] Other likely explanations include the short rest period between tests with partial metabolic recovery or perhaps a low motivation to repeat the test.[11] Interestingly, the use of the 6MWD from the 'best effort' test was recently criticized and the 6MWD obtained as the average of trials has been considered as more representative of the true value.[36] In this regard, the averaged 6MWD is not influenced by the order of the greater-distance test. Further studies are required to confirm if the decreasing trend in repetitive 6MWD is specific to patients with hypertension. Moreover, whether a single 6MWD[38] or multiple 6MWD are necessary for this population and, in the latter case, whether the proper outcome for the evaluation of cardiac rehabilitation programs is the 'best effort' or the averaged 6MWD still requires clarification.

Patients with hypertension presented lower 6MWD compared with sex-matched healthy controls, highlighting that the 6MWT captures the hemodynamic-related functional capacity of patients with hypertension. Personal variables (age, body height and weight) that are considered as risk factors for CVD also have an inverse effect on the 6MWD in patients with hypertension. It appears surprising that the same factors also affect the 6MWD in healthy controls. However, this is not contradictory because cardiovascular risk increases linearly with blood pressure values.[3,4] In addition, the large SD of the 6MWD observed in patients compared with healthy controls reflects the heterogeneity of phenotypes in hypertension itself. Accordingly, the systematic overestimation of the 6MWD by the Brazilian equations based on healthy controls can be explained by the low 6MWD values observed because of the adopted methods. However, the absence of a significant difference between groups in two out of three reference equations[26,27]—along with their low R^2—strongly suggests that equations derived from control groups are not capturing the statistical relationships between the 6MWD and clinical, and hemodynamic variables, which are population-specific.

Both groups presented values of the 6MWD that were somewhat lower than those of other studies.[18–21,23] The systematically low values are because of methodological factors known to affect negatively both groups simultaneously, including the smaller corridor and the lack of incentive phrases used during the test. The sex-match design of this study was selected because sex is a variable that is consistently correlated with the 6MWD,[11,15] with male subjects exhibiting higher values than female subjects in both studied groups. Body height, although not controlled, was not significantly different between groups and therefore exerted no directional influence on the 6MWD. Other uncontrolled variables in this study are known to negatively (higher age and body weight in the patient group)[11] and positively (higher physical activity level in the control group)[40] affect the 6MWD. Those differences in personal variables may contribute to a larger difference between groups but are unlikely to change the outcome of the study—the association between hemodynamic variables and functional capacity—although a reduction in statistical power may be expected because of the small sample size.[41] Most importantly, those differences comprise actual risk factors for CVD that are indeed more prevalent in patients with hypertension than in healthy controls.[5] Consequently, the hemodynamic-related functional capacity presented by patients and controls was indeed captured by the 6MWT and is reflected as the 6MWD.

The observed significant association values between the 6MWD and personal variables suggest that these variables influence the test outcome. The strengthening of the bivariate correlation between the 6MWD and hemodynamic variables in both groups after controlling for confounders further suggests their potential as predictors while reinforcing the internal validity of this study. Other studies also found a significant and inverse association between PP and 400-m gait speed in elderly subjects at risk for mobility disability, suggesting that hemodynamic parameters are associated with functional capacity tests, notwithstanding a self-paced gait.[42] On the basis of this interpretation, the inclusion of hemodynamic variables in equations for the prediction of the 6MWD appears justified. Most importantly, the significant association between hemodynamics and functional capacity in healthy subjects justifies the use of the 6MWT as a diagnostic routine test in the population at risk of developing CVD for the early recognition of impaired functional capacity. This clinical implication of this statement in primary preventive medicine is in agreement with the current trend in hypertension management of treating patients who have not yet manifested symptoms.[43]

A new trend is emerging in the development of the 6MWD prediction equations. Given the apparent limitation of the reference equations in adjusting between the real and predicted 6MWD, a new approach replaces the comparison 'patient–control' with 'patient–patient'. This new approach has already been applied for the derivation of a more specific equation for use in patients with Parkinson's disease. The outcomes from other tests specifically related to the pathophysiology of the disease—the Berg Balance Scale and TUG—were also identified as independent predictors along with weight, height, age and sex.[44,45] The 6MWD was also a marker of disability in patients with systemic sclerosis with disease-specific determinants of the 6MWD, such as disease activity and the Scleroderma Health Assessment Questionnaire score.[46] Similarly, the results of this study call for the further investigation of new prediction

Table 4 Unstandardized regression coefficients (95% confidence interval) on averaged 6MWD in patients with hypertension and healthy subjects

	Groups			
Independent variable	*Hypertension* (n = *41)*	P-*value*	*Healthy* (n = *41)*	P-*value*
Model no. 0	$R^2 = 0.522$	<0.001	$R^2 = 0.547$	<0.001
Sex	148.14 (77.16; 219.13)	<0.001	79.26 (25.28; 133.23)	0.005
Age	−1.52 (−3.86; 0.81)	0.194	−2.66 (−5.13; −0.20)	0.035
Height	−29.73 (−603.87; 544.41)	0.917	422.59 (10.33; 834.85)	0.045
Weight	0.80 (−1.25; 2.85)	0.434	−2.23 (−4.95; 0.50)	0.107
Model no. 4	$R^2 = 0.548$	<0.001	$R^2 = 0.512$	<0.001
Sex	131.55 (60.61; 202.48)	0.001	64.76 (11.71; 117.81)	0.018
Age	−1.45 (−3.72; 0.81)	0.201	−3.08 (−5.78; −0.38)	0.026
Height	137.56 (−341.57; 616.69)	0.564	291.46 (−101.97; 684.89)	0.142
PP	−1.42 (−3.16; 0.32)	0.106	−0.27 (−3.92; 3.38)	0.883
Model no. 1	$R^2 = 0.611$	<0.001	$R^2 = 0.548$	<0.001
Sex	116.91 (50.18; 183.64)	0.001	53.32 (0.46; 106.19)	0.048
Age	−1.49 (−3.59; 0.61)	0.158	−2.13 (−4.90; 0.29)	0.080
Height	188.29 (−257.90; 634.47)	0.398	360.04 (−27.64; 747.71)	0.068
SP	−1.99 (−3.33; −0.64)	0.005	−2.27 (−5.00; 0.45)	0.099
Model no. 2	$R^2 = 0.626$	<0.001	$R^2 = 0.561$	<0.001
Sex	125.32 (61.49; 189.15)	<0.001	50.80 (−1.45; 103.05)	0.056
Age	−1.53 (−3.59; 0.53)	0.140	−2.89 (−5.26; −0.53)	0.018
Height	158.13 (−276.45; 592.71)	0.465	385.02 (−0.14; 770.18)	0.050
DP	−4.56 (−7.37; −1.75)	0.002	−3.34 (−6.71; 0.04)	0.053
Model no. 3	$R^2 = 0.648$	<0.001	$R^2 = 0.565$	<0.001
Sex	113.83 (50.62; 177.04)	0.001	49.14 (−3.20; 101.48)	0.065
Age	−1.53 (−3.53; 0.47)	0.130	−2.54 (−4.95; −0.12)	0.040
Height	198.21 (−225.87; 622.29)	0.349	391.78 (7.48; 776.09)	0.046
MP	−4.09 (−6.33; −1.85)	0.001	−3.49 (−6.88; −0.10)	0.044

Abbreviations: 6MWD, six-minute walk distance; DP, diastolic pressure; MP, mean pressure; PP, pulse pressure; SP, systolic pressure.
Age, years; DP, mm Hg; height, meters; sex, male = 1; MP, mm Hg; PP, mm Hg; SP, mm Hg; weight.

equations based on the hemodynamic variables associated with the 6MWD, mainly MP because of its higher significant correlation and adjusted R^2 in the models evaluated. To this end, a large sample of adults with hypertension presenting different phenotypes and other risk factors for CVD should be studied to determine a specific prediction equation for this population to be used as an outcome of cardiac rehabilitation programs.

Some study limitations deserve consideration regarding the interpretation of the results. All patients were under antihypertensive treatment with different combinations of medication classes and dosages, and thus drug effects on blood pressure levels and performance could not be investigated. Although blood pressure levels could be corrected to account for this, this was not performed because a constant correction factor would not change the observed associations. Nevertheless, the studied sample included patients with grade I–II hypertension despite drug therapy, which is likely to result from resistant hypertension or suboptimal medication regimens that were still under adjustment.[47] Therefore, the observed results are considered representative for medicated patients and should not be extrapolated to untreated patients without proper evidence. In addition, the finding of the highest observed R^2 value in model no. 3 suggests that other variables such as physical activity level and HR could be used to improve the prediction of the 6WMD. However, because of the sample size that would be required, this evaluation was not performed in our study and is recommended for future studies. Notably, we did not assess indices of left ventricular function (for example, stroke volume) that are correlated to the 6MWD in patients with heart failure,[48] and as such, this might represent a confounder of our results. Finally, the cause–effect relationship between hemodynamic variables and the 6MWD cannot be assessed in this study. Case–control designs do not allow causal inference (that is, the increase in hemodynamic variables decreases the 6MWD and a decrease in hemodynamic variables increases the 6MWD *per se*) owing to a possible cause-and-effect reversal, and thus the results must be interpreted accordingly.

In summary, our study demonstrated that the 6MWD is inversely associated with hemodynamic variables in both groups and is lower in patients with hypertension compared with healthy controls. Hemodynamic variables, particularly the MP, should be included in prediction equations for 6MWD under the concept of 'patient–patient' comparison.

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