

Beneficial effect of antihypertensive therapy on exercise capacity assessed by a 6-minute walk test at one year follow-up

Korzystny wpływ terapii hipotensyjnej na zdolność do wykonania wysiłku
ocenianą w 6-minutowym teście marszowym w obserwacji rocznej

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Lekarz Małgorzata Kurpaska jest absolwentką Wydziału Lekarskiego Uniwersytetu Medycznego w Lublinie. Obecnie odbywa szkolenie specjalizacyjne z chorób wewnętrznych w Klinice Kardiologii i Chorób Wewnętrznych Wojskowego Instytutu Medycznego w Warszawie pod kierownictwem dra hab. n. med. Pawła Krześcińskiego. Zainteresowania naukowe dr Kurpaski skupiają się wokół wydolności fizycznej oraz zastosowania nieinwazyjnych metod, takich jak kardiografia impedancyjna czy tonometria aplanacyjna, w monitorowaniu profilu hemodynamicznego w trakcie wysiłku fizycznego. Czas wolny wypełnia jej rodzina.

Abstract

Introduction. Individual variation of exercise tolerance may be clinically important even in asymptomatic patients with arterial hypertension (HTN). The aim of the study was to evaluate the effect of antihypertensive therapy on exercise capacity assessed by a 6-minute walk test (6-MWT) and its relation to selected clinical and hemodynamic parameters.

Material and methods. In a group of 111 hypertensive patients without symptoms of heart failure, the change in 6-MWT distance (d_{6-MWT}) after 12 months of antihypertensive therapy was assessed in relation to their clinical status and hemodynamic parameters, assessed by echocardiography, impedance cardiography, and applanation tonometry.

Results. In the overall study group, antihypertensive therapy was associated with a significant increase in the mean d_{6-MWT} (592.9 ± 72.8 vs 613.4 ± 66.0 m, p = 0.030). The change in d_{6-MWT} depended on baseline values, with the most significant improvement (mean by 63.4 m) observed in patients with initially lowest d_{6-MWT} (bottom quartile, < 530 m). No statistically significant correlations were found between d_{6-MWT} and changes in clinical and hemodynamic parameters. However, trends were noted towards positive associations between d_{6-MWT} and an echocardiographic indicator of left ventricular filling pressure (E/e'), left ventricular ejection fraction, and stroke index.

Conclusions. Antihypertensive therapy improves exercise capacity in hypertensives with initially reduced exercise capacity, and this effect may be related to positive changes in the left ventricular systolic and diastolic function.

Key words: impedance cardiography, applanation tonometry, hypertension, left ventricular diastolic dysfunction, 6-minute walk test

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Introduction

Unspecific reduction of exercise tolerance is a subjective symptom, often neglected by both patients and healthcare personnel. Reduced exercise capacity depends not only on the cardiovascular status but also constitutional factors, condition of the skeletal muscle, and respiratory function [1]. In patients with hypertension (HTN), progressive cardiovascular dysfunction is a continuous process, and the importance of subclinical abnormalities is often underestimated. Cardiac remodelling associated with increased blood pressure (BP) and arterial stiffness usually leads first to left ventricular diastolic dysfunction [1–3] and only at a more advanced stage to reduced left ventricular ejection fraction (LVEF) and overt heart failure [4, 5]. Apparently mild reduction of left ventricular compliance at rest may manifest with significant pressure overload of the pulmonary circulation during exercise, limiting tolerance of the latter [2, 6].

It is thus worth looking for simple, non-invasive hemodynamic assessment tools in patients with reduced exercise tolerance at the early stage of hypertensive heart disease that might provide data on the potential underlying pathomechanisms and would be useful for the monitoring of treatment effects. We have previously found that multiparameter assessment of the cardiovascular system function by echocardiography and impedance cardiography (ICG) may be useful for the identification of hemodynamic abnormalities associated with reduced exercise capacity [7]. Based on these findings, we hypothesized that these methods may also be useful to evaluate the relations between antihypertensive treatment-induced changes in the hemodynamic profile and exercise capacity evaluated by 6-minute walk test (6-MWT).

Thus, the aim of our study was to evaluate the effect of antihypertensive treatment on exercise capacity evaluated by 6-MWT and to correlate this effect with selected clinical and hemodynamic parameters.

Material and methods

Study group

The study was conducted in 139 asymptomatic patients of both genders with untreated HTN (with elevated BP values for ≥ 3 months) at a moderate level of physical activity. The baseline characteristics of the study group are shown in Table 1. The exclusion criteria were: 1) confirmed secondary HTN; 2) confirmed stage 3 or higher chronic kidney disease (glomerular filtration rate [GFR] < 60 mL/min/1.73 m² by the Modification of Diet in Renal Disease Study [MDRD] formula); 3) other severe concomitant conditions such as systolic heart failure, cardiomyopathy, significant arrhythmia, significant valvular heart disease, chronic obstructive

pulmonary disease, diabetes, polyneuropathy, and peripheral arterial disease; age younger than 18 or older than 75 years; 5) body mass index (BMI) above 40 kg/m²; 6) mental disorders precluding adequate patient compliance; and 7) cardiac rhythm other than sinus rhythm (including permanent cardiac pacing).

The study protocol was approved by the bioethics committee at the Military Institute of Medicine (Wojskowy Instytut Medyczny [WIM], approval No. 3/WIM/2008), and each patient gave a written consent for the study participation. The study was performed under a WIM statutory research project (ID 148) undertaken in the Department of Cardiology and Internal Medicine, Military Institute of Medicine, and registered in the ClinicalTrials.gov database (NCT01996085).

The effect of antihypertensive therapy was evaluated in 111 subjects who attended the follow-up visit at 12 months. The analysis included clinical examination and hemodynamic parameters evaluated noninvasively using echocardiography, ICG, and applanation tonometry.

Clinical examination

Clinical examination was conducted with a particular focus on the history of cardiovascular risk factors. The presence of metabolic syndrome was defined according to the current International Diabetes Federation (IDF) guidelines [8]. The final analysis included the change in resting heart rate (HR) [bpm], systolic blood pressure (SBP) [mm Hg], and diastolic blood pressure (DBP) [mm Hg].

Six-minute walk test

Exercise capacity was evaluated during 6-MWT. The patients had been instructed to walk as fast as they could

Table 1. Baseline characteristics of the study group

Variable	Study group (N = 139)
Age [years], mean \pm SD	45.6 \pm 10.3
Men, n [%]	96 (69.1)
Stage 1 HTN*, n [%]	112 (79.2)
Stage 2 HTN*, n [%]	27 (19.4)
SBP [mm Hg], mean \pm SD	141 \pm 13
DBP [mm Hg], mean \pm SD	90 \pm 9
HR [bpm], mean \pm SD	72 \pm 10
BMI [kg/m ²], mean \pm SD	29.0 \pm 4.2
LVH, n [%]	15 (10.8)
LVDD, n [%]	35 (25.2)
MS, n [%]	81 (58.3)

*According to the 2013 European Society of Hypertension/European Society of Cardiology guidelines classification of hypertension (HTN) [9]; SD – standard deviation; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; BMI – body mass index; LVH – left ventricular hypertrophy; LVDD – left ventricular diastolic dysfunction; MS – metabolic syndrome

at a comfortable pace along a 25-meter-long corridor marked every 5 meters. The total distance covered over 6 minutes was rounded to 5 meters. All patients were evaluated for dyspnoea, chest pain, and palpitation during the test.

Echocardiography

Echocardiographic examinations were performed using a Vivid S6 system (GE Medical System, Wauwatosa, WI, USA). Evaluation included cardiac chamber size, left ventricular systolic and diastolic function, and valvular structure and function. Left ventricular hypertrophy (LVH) was diagnosed based on the evaluation of left ventricular mass (LVM) indexed for body surface (left ventricular mass index [LVMI] > 95 g/m² in women, > 115 g/m² in men). Left ventricular mass was calculated using the following formula: $LVM = 0.8 \times (1.04 \times [LVEDD + PWTd + SWTd]^3 - [LVEDD]^3) + 0.6$ [g], where LVEDD is left ventricular end-diastolic diameter [mm], PWTd is diastolic posterior wall thickness [mm], and SWTd is diastolic septal wall thickness [mm]. Measurements of the variables required for calculation, i.e. LVEDD, PWTd, and SWTd, were made in the long-axis parasternal view in M-mode, guided by two-dimensional (2D) imaging. Left ventricular ejection fraction [%] was measured using the Simpson method.

Left ventricular diastolic dysfunction was diagnosed based on the current guidelines [9] as reported previously [7]. Mitral flow was evaluated by pulsed wave Doppler in the apical four-chamber view, with measurement of the E wave deceleration time [ms] and the early to atrial filling velocity ratio (E/A). Using tissue Doppler imaging (TDI), early diastolic mitral annulus velocity (e') [cm/s] was measured and the E/e' ratio [cm/s] was calculated. In the apical 5-chamber view, simultaneous assessment of the aortic and mitral flow was possible, with calculation of the isovolumetric relaxation time (IVRT) [ms]. The following values were considered diagnostic for left ventricular diastolic dysfunction: left atrial dimension above 40 mm in men, above 38 mm in women, E/A ratio below 0.8, E wave deceleration time above 200 ms, IVRT equal to or greater than 100 ms, e' below 8 cm/s, E/e' ratio above 8. Only the mild form of left ventricular diastolic dysfunction, i.e. impaired relaxation, was found.

Impedance cardiography

Hemodynamic parameters were measured by ICG during a 10-minute resting examination in a supine position, using a Niccomo™ device (Medis, Ilmenau, Germany). The final analysis included the following parameters: stroke index (SI) [mL × m⁻²], cardiac index (CI) [mL × m⁻² × min⁻¹], systemic vascular resistance index (SVRI) [dyn × s × cm⁻⁵ × m²], total arterial compliance (TAC) [mL × mm Hg⁻¹], velocity index

(VI) [1000 × ZO × s⁻¹], acceleration index (ACI) [100 × ZO × s⁻²], and thoracic fluid content (TFC) [L × kΩ⁻¹].

Central blood pressure measurement

Central BP was measured noninvasively by applanation tonometry (SphygmoCor PxAortic BP Profile System, AtCor Medical Pty Ltd, Australia). Measurements were performed at the left radial artery in a supine position using a micromanometer (Millar Instruments, Houston, Texas, USA) following the resting ICG examination. SphygmoCor 2000 software (version 7.01; AtCor Medical) was used for pulse wave analysis. The following parameters were analysed: central systolic blood pressure (CSBP) [mm Hg], central diastolic blood pressure (CDBP) [mm Hg], central pulse pressure (CPP) [mm Hg], and augmentation index (AI) [%].

Drug treatment

Non-drug treatment was consistent with the current 2013 European Society of Hypertension/European Society of Cardiology guidelines [10]. Drug treatment was based on the methods used in the FINEPATH study (NCT01996085) [11]. Patients received at least one of the following drugs: lisinopril (ACEI, angiotensin-converting enzyme inhibitor), telmisartan (ARB, angiotensin receptor blocker), hydrochlorothiazide/indapamide (diuretic), metoprolol/nebivolol (BB, beta-blocker), amlodipine (CCB, calcium channel blocker).

Statistical analysis

Statistical analysis was performed using Microsoft Office Excel 2007 and Statistica 10.0 (StatSoft Inc.) software. Results were expressed as mean values ± standard deviation (SD) for quantitative variables and numbers and percentages for qualitative variables. Variable distribution was assessed visually and using the Kolmogorov-Smirnov test. Correlations were evaluated using the Pearson correlation coefficient for normally distributed variables and the Spearman rank correlation coefficient for non-normally distributed variables.

Change in a variable (d) was calculated using the formula: $\text{change } (d_{[\text{variable}]}) = \text{value at 12 months } (c_{[\text{variable}]}) - \text{baseline value } (b_{[\text{variable}]})$.

First, the interquartile range of baseline 6-MWT (b₆-MWT) [7] was used to evaluate the effect of antihypertensive treatment on the change in 6-MWT (d₆-MWT). Then, to differentiate between changes in clinical and hemodynamic parameters in relation to d₆-MWT, the interquartile range was calculated for that variable (Q1: < [-35] m; Q2: [-35] - [13] m; Q3: [14] - [73] m; Q4: > [73] m) and a comparative analysis was performed in quartile subgroups (ANOVA or Kruskal-Wallis tests depending on variable distribution). P < 0.05 was considered statistically significant.

Table 2. Parameters at baseline and after 12 months of antihypertensive therapy

Variable	Mean	Minimum	Maximum	Standard deviation
b_6-MWT [m]	592.9459	400.0000	750.0000	72.77410
c_6-MWT [m]	613.3514	415.0000	760.0000	65.99265
b_HR [bpm]	73.0463	49.0000	99.0000	10.64322
c_HR [bpm]	67.6937	46.0000	89.0000	8.53740
b_SBP [mm Hg]	141.0180	111.0000	180.0000	13.18469
b_DBP [mm Hg]	90.0088	62.0000	122.0000	9.42075
c_SBP [mm Hg]	120.1261	98.0000	157.0000	9.60314
c_DBP [mm Hg]	76.9730	55.0000	94.0000	7.38852
b_E/A [-]	1.0559	0.5500	2.1000	0.32890
c_E/A [-]	1.1609	0.5200	2.1400	0.34031
b_e' [cm/s]	9.6132	4.0000	15.5000	2.64601
c_e' [cm/s]	10.3364	5.0000	17.0000	2.44303
b_E/e' [-]	7.1780	4.3000	13.0000	1.73839
c_E/e' [-]	6.9757	4.0600	13.8000	1.76113
b_LVEF [%]	64.8818	56.0000	72.0000	3.18463
c_LVEF [%]	66.3545	59.0000	75.0000	3.24980

b_variable – baseline value; c_variable – value at 12 months of treatment; 6-MWT – 6-minute walk test; HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; e' – peak mitral annular velocity; E/e' – early mitral inflow velocity to mitral annular velocity ratio; E/A – early to atrial mitral inflow velocity ratio; LVEF – left ventricular ejection fraction

Results

Effect of treatment on 6-MWT distance

Final analysis included 111 patients who completed one year follow-up. Antihypertensive treatment was associated with a significant increase in the mean 6-MWT distance (592.9 ± 72.8 vs. 613.4 ± 66.0 m, $p = 0.030$) in the overall study group. A significant reduction was also seen in SBP (141.0 ± 13.2 vs. 120.1 ± 9.6 mm Hg, $p < 0.00001$), DBP (90.0 ± 9.4 vs. 77.0 ± 7.4 mm Hg, $p < 0.0001$), and HR (73.0 ± 10.6 vs. 67.7 ± 8.5 bpm, $p = 0.00005$; Table 2).

The change in 6-MWT distance was related to the baseline 6-MWT distance (b_6-MWT). The largest improvement was seen in patients with the lowest 6-MWT distance at baseline (bottom b_6-MWT quartile, < 530 m), in contrast to those with the highest 6-MWT distance at baseline (upper b_6-MWT quartile, > 650 m, Figure 1). When individual changes were plotted (Figure 2), a highly consistent trend was seen for an improvement in 6-MWT distance in those in the bottom b_6-MWT quartile, while a reverse trend was seen in those in the upper b_6-MWT quartile.

Associations between 6-MWT distance change and changes in other parameters

We did not find any significant correlations between d_6-MWT and changes in other analysed clinical and hemodynamic variables (Table 3). However, trends were seen towards a positive association between d_6-MWT and a reduction in E/e' and an increase in LVEF, SI, and

TFC, as well as for a higher rate of metabolic syndrome in subjects with no improvement in 6-MWT distance. No significant differences in drug therapy were found between d_6-MWT quartiles.

Discussion

Our study findings confirm that effective antihypertensive treatment is associated with an increase in the mean 6-MWT distance. This effect is most pronounced in subjects with most limited exercise capacity at baseline. Hemodynamic evaluation at rest has a limited value regarding identification of hemodynamic determinants of the change in the mean 6-MWT distance. However, the observed trend for an association between improvement in exercise capacity and reduced left ventricular filling pressure and improved left ventricular systolic function seems promising.

An increase in 6-MWT distance related to BP lowering by various antihypertensive drug classes has been confirmed in studies by other authors [12, 13]. Thus, variation in exercise capacity in patients with HTN is not an incidental finding, although these subjects often do not report other heart failure symptoms. The most significant improvement in 6-MWT distance observed in those with the worst exercise tolerance at baseline confirms that by using an objective diagnostic tool, it is possible to identify asymptomatic (based on a subjective patient's assessment) reduction in exercise capacity that may be favourably modified by a therapeutic intervention.

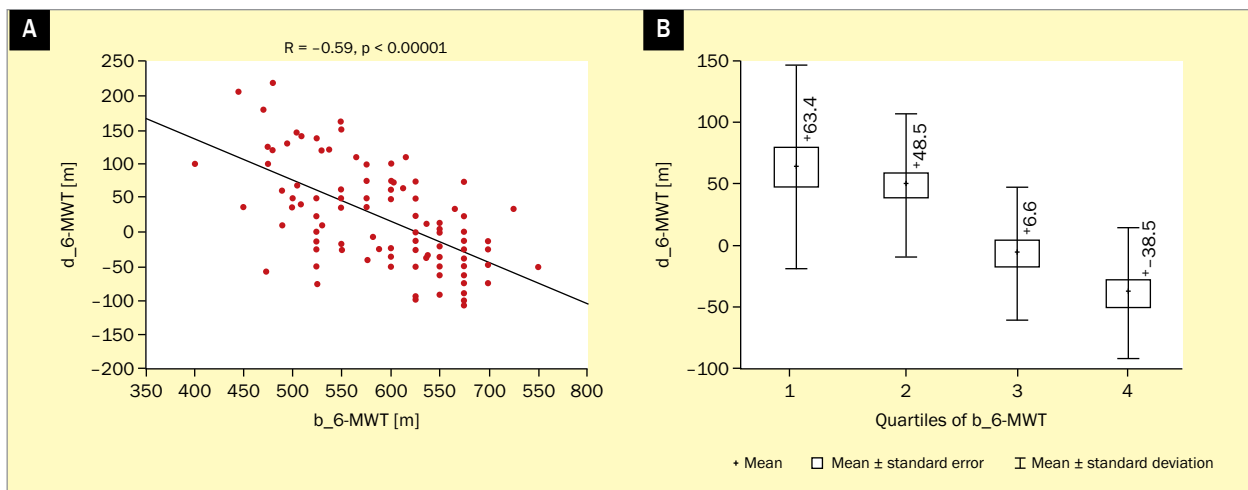


Figure 1A, B. Relation between the change in 6-minute walk test distance (d_6-MWT) and its baseline value (b_6-MWT): **A.** Scatter and correlation of d_6-MWT vs. b_6-MWT; **B.** Comparison of d_6-MWT by quartiles of b_6-MWT ($p < 0.000001$)

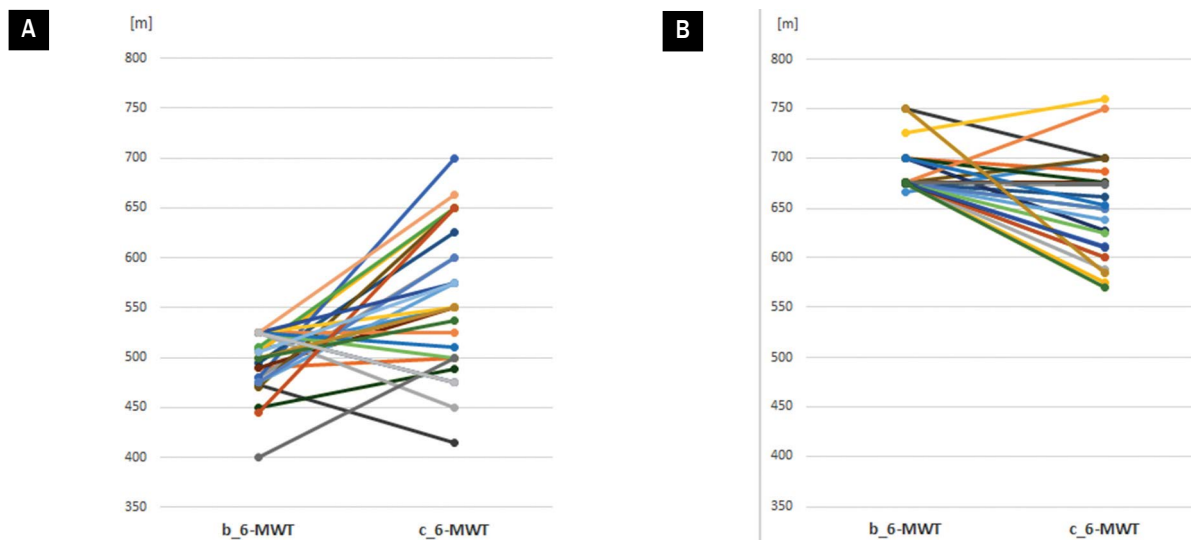


Figure 2A, B. Comparison of individual values of 6-minute walk test distance (6-MWT) in two extreme b_6-MWT quartiles: **A.** Bottom quartile; **B.** Upper quartile; b_6-MWT – baseline 6-MWT distance; c_6-MWT – 6-MWT distance after 12 months

In our study, we did not find differences between various drugs used. This may be related to the design of the study which evaluated an overall treatment effect and not particular drug classes. The observed worse treatment in subjects with metabolic syndrome may be related to constitutional limitations and more advanced hemodynamic abnormalities at baseline [14, 15].

Despite multiparametric assessment of the hemodynamic profile, we did not identify any predominant mechanism responsible for the observed improvement in exercise capacity. Based on our previous study, in which we showed an association between 6-MWT distance and

elevated parameters of large vessel stiffness [7], we expected a more evident association between changes in 6-MWT distance and afterload changes (SVRI, TAC, AI). Nevertheless, the observed trends for an association between the increase in 6-MWT distance and reduction of an echocardiographic indicator of diastolic function (E/e'), increase in LVEF, and increase in SI by impedance cardiography is consistent with our knowledge regarding cardiovascular pathophysiology. Exercise capacity is related to ventricular-vascular coupling. During exercise, blood flow in various vascular beds is redistributed towards skeletal muscle. Significant changes in vascular

Table 3. Relations between the change in 6-minute walk test (6-MWT) distance and other variables

Variable	6-MWT (quartiles)				p (overall)	Correlation variable vs. d_6-MWT	
	Q1 (N = 27)	Q2 (N = 28)	Q3 (N = 26)	Q4 (N = 28)		R	p (overall)
Demographic and clinical characteristics							
Age [years]	46.0 ± 10.9	46.7 ± 11.5	48.3 ± 9.6	45.2 ± 8.6	0.722	0.02	0.861
Male gender	20 (71.4)	19 (65.5)	18 (69.2)	20 (71.4)	0.957	-	-
BMI [kg/m ²]	29.9 ± 3.7	28.9 ± 3.7	28.4 ± 4.3	28.8 ± 4.0	0.596	-0.09	0.360
MS	21 (75.0)	17 (58.6)	13 (50.0)	14 (50.0)	0.191	-	-
Office measurements							
d_HR [bpm]	-3.6 ± 8.2	-4.9 ± 9.6	-7.4 ± 13.1	-6.0 ± 11.0	0.876	-0.08	0.427
d_SBP [mm Hg]	-22.5 ± 14.2	-20.9 ± 12.6	-18.0 ± 13.1	-21.9 ± 14.1	0.667	0.02	0.800
d_DBP [mm Hg]	-15.1 ± 8.9	-11.9 ± 10.6	-12.5 ± 8.3	12.6 ± 9.9	0.693	0.06	0.558
Echocardiography							
d_LVEF [%]	1.3 ± 4.3	0.3 ± 4.2	2.3 ± 4.2	2.3 ± 3.8	0.245	0.14	0.155
d_E/A [-]	0.14 ± 0.34	0.10 ± 0.37	0.12 ± 0.23	0.05 ± 0.28	0.671	-0.03	0.759
d_e' [cm/s]	0.74 ± 2.68	0.57 ± 2.56	1.17 ± 2.35	0.75 ± 2.66	0.854	0.01	0.958
d_E/e' [-]	-0.22 ± 1.65	0.11 ± 2.09	-0.28 ± 1.62	-0.84 ± 1.67	0.294	-0.13	0.171
Impedance cardiography							
d_SI [mL/m ²]	0.3 ± 8.3	1.8 ± 9.6	3.2 ± 7.9	3.6 ± 9.8	0.527	0.16	0.096
d_CI [mL/min/m ²]	-0.17 ± 0.47	-0.2 ± 0.56	-0.10 ± 0.51	-0.01 ± 0.41	0.623	0.07	0.473
d_SVRI [dyn × s/cm ⁵ /m ²]	-251 ± 342	-318 ± 494	-164 ± 506	-247 ± 319	0.615	0.04	0.653
d_ACI [100 × Z0/s ²]	2.3 ± 22.3	0.1 ± 18.0	5.9 ± 16.6	5.2 ± 21.9	0.690	0.07	0.453
d_VI [1000 × Z0/s]	1.3 ± 10.0	0.2 ± 10.2	3.1 ± 8.8	3.7 ± 10.3	0.783	0.11	0.274
d_TAC [mL/mm Hg]	0.21 ± 0.57	0.39 ± 0.56	0.32 ± 0.61	0.39 ± 0.65	0.640	0.04	0.653
d_TFC [L/kOhm]	-0.5 ± 3.2	-0.1 ± 3.4	0.1 ± 4.3	1.3 ± 3.6	0.251	0.19	0.052
Applanation tonometry							
d_CSBP [mm Hg]	-186 ± 15.9	-15.1 ± 12.9	-17.0 ± 14.3	-12.5 ± 14.4	0.429	0.12	0.202
d_CDBP [mm Hg]	-14.4 ± 9.6	-10.2 ± 10.2	-12.4 ± 8.9	-10.4 ± 8.9	0.461	0.10	0.297
d_CPP [mm Hg]	-4.2 ± 9.4	-4.9 ± 7.5	-4.6 ± 9.2	-2.5 ± 9.3	0.561	0.09	0.332
d_AI [%]	-0.7 ± 12.2	-0.9 ± 7.7	-1.2 ± 11.9	2.4 ± 11.4	0.846	0.06	0.523
Drug therapy							
ACEI	21 (77.8)	21 (75.0)	20 (80.0)	19 (67.9)	0.751	-	-
ARB	2 (7.4)	4 (14.3)	2 (8.0)	5 (17.9)	0.581	-	-
CCB	5 (18.5)	6 (21.4)	5 (20.0)	1 (3.6)	0.230	-	-
BB	7 (25.9)	4 (14.3)	8 (32.0)	7 (25.0)	0.495	-	-
Diuretic	7 (25.9)	8 (28.6)	9 (36.0)	9 (32.1)	0.872	-	-

Data shown as mean values ± standard deviation (SD) or numbers (percentages); BMI – body mass index; MS – metabolic syndrome; d_HR – change in heart rate; d_SBP – change in systolic blood pressure; d_DBP – change in diastolic blood pressure; LVEF – left ventricular ejection fraction; d_LVEF – change in left ventricular ejection fraction; d_e' – change in peak mitral annular velocity; d_E/A – change in the early to atrial mitral inflow velocity ratio; d_E/e' – change in the early mitral inflow velocity to mitral annular velocity ratio; d_SI – change in the stroke index; d_CI – change in the cardiac index; d_SVRI – change in the systemic vascular resistance index; d_ACI – change in the acceleration index; d_VI – change in the velocity index; d_TAC – change in total arterial compliance; d_TFC – change in thoracic fluid content; d_CSBP – change in central systolic blood pressure; d_CDBP – change in central diastolic blood pressure; d_CPP – change in central pulse pressure; d_AI – change in the augmentation index; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; CCB – calcium channel blocker; BB – beta-blocker

resistance lead to a reduction in afterload, allowing an increase in cardiac output [16]. In contrast, an increase in aortic and large vessel stiffness results in left ventricular pressure overload which precludes adequate adjustment of cardiac output to match exercise-induced requirements [17]. In several previous studies, a significant inverse correlation was shown between markers of vascular stiffness (e.g., pulse wave velocity) with peak oxygen consumption (peakVO_2) and 6-MWT distance [18–20]. With BP reduction, afterload is reduced and blood is ejected at a higher velocity from the left ventricle to a more compliant vascular system. Ultimately, more blood is ejected (an increase in SI) which results in a reduced end-systolic volume (ESV). In turn, lower ESV allows for an increased volume reservoir for venous return and thus left ventricular filling pressure is reduced [16]. Our study findings support the notion that treatment that aims to normalize vascular stiffness, left ventricular diastolic function, and increased left ventricular mass may be of no less importance than BP reduction per se [21, 22]. We previously noted [23] that left ventricular diastolic dysfunction coexists with subclinical left ventricular systolic dysfunction as measured by global longitudinal strain (GLS). Improvement in left ventricular diastolic function correlated significantly with improvement in GLS (GLS vs. e' : $r = -0.51$, $p < 0.001$; GLS vs. E/e' : $r = 0.23$, $p = 0.022$) [24]. This explains why diastolic dysfunction at rest may be a harbinger of more severe hemodynamic disturbance associated with exercise. Palmieri et al. [2] examined this phenomenon and showed an association between diastolic dysfunction and impaired increase in CI and SI during exercise, which reduces exercise capacity in still asymptomatic patients.

The observed trend for an increase in TFC related to increased 6-MWT distance should not be interpreted as a positive effect of fluid retention. Previous studies in this population [25, 26] suggest that among middle-aged subjects with uncomplicated HTN, baseline TFC may be reduced compensatory to increased afterload. Thus afterload reduction secondary to BP lowering may result in an increase in TFC due to normalization of the hemodynamic profile.

When interpreting our study findings, it is important to consider potential factors affecting the change in 6-MWT distance independently from the body's functional status. In our opinion, contribution of the „learning effect” seen at 2 months of follow-up [27, 28] was marginal. First, 6-MWT distance was re-evaluated at 12 months of treatment. Second, individual effects varied, and changes in many patients were larger than the previously reported 6% change attributed to this phenomenon [27, 28]. In turn,

the competition effect (resulting in an increase in 6-MWT distance by 20–30%) [29] was eliminated by performing these examinations individually.

Study limitations

A limitation of our study was the size of the study group which may have resulted in no significance of the association between d_6 -MWT and changes in the analyzed clinical and hemodynamic parameters. An analysis limited to subjects with hypertension and no concomitant conditions has eliminated an effect of confounding factors but it also precludes direct generalization of the study findings to the general population. Due to a progressive nature of hypertensive heart disease, a more evident improvement in exercise tolerance might be expected during longer follow-up and in patients with stage 3 HTN at baseline. Of note, further studies with hemodynamic monitoring during exercise are needed to expand our knowledge regarding the mechanisms of the observed improvement in exercise capacity.

The authors believe, however, that the above limitations have had no significant effect on the overall value of the study.

Conclusions

Antihypertensive treatment in patients with hypertension and no overt heart failure improves exercise tolerance. Particularly beneficial effects were observed in subjects with limited exercise capacity at baseline. Non-invasive tools to evaluate hemodynamic parameters, particularly echocardiography and impedance cardiography, are useful for the assessment of hemodynamic response to exercise, including when monitoring the effects of antihypertensive treatment.

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Conflicts of interest(s)

The authors declare no conflicts of interests related to the article.

Streszczenie

Wstęp. Indywidualne zróżnicowanie tolerancji wysiłku fizycznego może mieć istotne znaczenie kliniczne już pacjentów z nadciśnieniem tętniczym (HTN) bez objawów. Celem pracy była ocena wpływu terapii hipotensyjnej na zdolność do wykonania wysiłku ocenianą w teście 6-minutowego marszu (6-MWT) oraz powiązania tego efektu z wybranymi parametrami klinicznymi i hemodynamicznymi.

Materiał i metody. W grupie 111 chorych z HTN i bez jawnych objawów niewydolności serca oceniono zmianę dystansu 6-MWT (d₆-MWT) po 12 miesiącach od rozpoczęcia leczenia hipotensyjnego w powiązaniu ze stanem klinicznym oraz parametrami hemodynamicznymi uzyskanymi za pomocą echokardiografii, kardiografii impedancyjnej i tonometrii aplanacyjnej.

Wyniki. W analizie w całej grupie leczenie hipotensyjne wiązało się z istotnym wydłużeniem średniego dystansu 6-MWT: 592,9 ± 72,8 v. 613,4 ± 66,0 m; p = 0,030. Zmiana dystansu 6-MWT zależała od wartości wyjściowych. Najwyraźniejszą poprawę zaobserwowano wśród chorych, którzy wyjściowo pokonali najkrótszy dystans 6-MWT (dolny kwartyl 6-MWT < 530 m), tj. 63,4 m. Nie wykazano istotnych statystycznie powiązań d₆-MWT ze zmianami analizowanych parametrów klinicznych i hemodynamicznych, choć obserwowano oczekiwany trend w kierunku pozytywnej korelacji d₆-MWT z obniżeniem echokardiograficznego wskaźnika ciśnienia napełniania (E/e') oraz zwiększeniem frakcji wyrzutowej lewej komory i kardioimpedancyjnego wskaźnika wyrzutowego.

Wnioski. Leczenie hipotensyjne poprawia tolerancję wysiłku fizycznego u pacjentów z niższą wydolnością fizyczną, co może się wiązać z poprawą funkcji skurczowej i rozkurczowej lewej komory.

Słowa kluczowe: kardiografia impedancyjna, tonometria aplanacyjna, nadciśnienie tętnicze, dysfunkcja rozkurczowa lewej komory, test 6-minutowego marszu

Folia Cardiologica 2018; 13, 2: 128–136

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