

Lower Physical Fitness in Patients With Primary Aldosteronism Is Linked to the Severity of Hypertension and Kalemia

V. TUKA¹, M. MATOULEK¹, T. ZELINKA², J. ROSA², O. PETRÁK², O. MIKEŠ¹, Z. KRÁTKÁ², B. ŠTRAUCH², R. HOLAJ², J. WIDIMSKÝ Jr.²

¹Centre of Cardiovascular Rehabilitation, Third Department of Medicine – Department of Endocrinology and Metabolism of the First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic, ²Centre for Hypertension, Third Department of Endocrinology and Metabolism of the First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

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Summary

Hypokalemia as a typical feature of primary aldosteronism (PA) is associated with muscle weakness and could contribute to lower cardiopulmonary fitness. The aim of this study was to describe cardiopulmonary fitness and exercise blood pressure and their determinants during a symptom-limited exercise stress test in patients with PA. We performed a cross-sectional study of patients with confirmed PA who were included before adrenal vein sampling on whom a symptom-limited exercise stress test with expired gas analysis was performed. Patients were switched to the treatment with doxazosin and verapamil at least two weeks before the study. In 27 patients (17 male) the VO_{2peak} was 25.4 ± 6.0 ml/kg/min which corresponds to 80.8 ± 18.9 % of Czech national norm. Linear regression analysis shows that VO_{2peak} depends on doxazosin dose (DX) ($p=0.001$) and kalemia ($p=0.02$): $VO_{2peak} = 4.2 - 1.0 * DX + 7.6 * Kalemia$. Patients with higher doxazosin doses had a longer history of hypertension and had used more antihypertensives before examination, thus indicating that VO_{2peak} also depends on the severity of hypertension. In patients with PA, lower cardiopulmonary fitness depends inversely on the severity of hypertension and on lower plasma potassium level.

Key words

Primary hyperaldosteronism • Physical fitness • Exercise blood pressure • Exercise stress test

Corresponding author

V. Tuka, Third Department of Internal Medicine, General University Hospital in Prague, U Nemocnice 1, 128 08, Prague 2, Czech Republic. Fax: +420 224 919 780. E-mail: Vladimir.Tuka@vfn.cz

Introduction

Primary aldosteronism (PA) is a syndrome of autonomous aldosterone production which is accompanied by hypertension and lower plasma potassium level (Gordon 1995, Galati 2015). PA is associated with increased cardiovascular morbidity compared to patients with a matched degree of hypertension (Catena *et al.* 2008, Savard *et al.* 2013).

Although hypokalemia is not found in all subjects with PA, decreased levels of serum potassium, reaching at least the lower reference limit, are found in the vast majority of patients with PA (Šomlóová *et al.* 2016). The effect of hypokalemia includes easy fatigability and muscle weakness (Gennari 1998) and approximately 40 % of patients with PA, especially in oriental countries, have musculoskeletal symptoms ranging from mild muscle weakness to paralysis or plegia (Huang *et al.* 1996). The muscle weakness with fatigue could decrease the habitual physical activity and level of exercise. Low habitual physical activity is associated with low physical fitness (McArdle *et al.* 2010).

Cardiopulmonary fitness depends on the ability of the heart to deliver oxygen to working muscles, thus on peak cardiac output (McArdle *et al.* 2010). Among several factors affecting cardiac output, afterload is blood pressure (BP) dependent. Essentially, arterial hypertension is associated with lower peak oxygen uptake (VO_{2peak}) and the antihypertensive treatment increases VO_{2peak} (Missault *et al.* 1992). As resting BP is increased in patients with PA, it can be hypothesised that they will also have an inadequately increased BP during exercise and thus have a decreased VO_{2peak} . In the general population and in different subpopulations, cardiopulmonary fitness is the best predictor of morbidity and mortality (Fleg 2012). To our best knowledge, there are no available data on cardiopulmonary fitness in patients with PA.

The aim of our study was to describe cardiopulmonary fitness and exercise blood pressure and their determinants during a symptom-limited exercise stress test in patients with PA. The hypothesis was that, due to hypokalemia and muscle weakness and to the severity of hypertension, cardiopulmonary fitness would be reduced.

Material and Methods

Study population

A cross-sectional study of patients with PA was performed. Between May 2013 and October 2014, consecutive patients with laboratory confirmed primary aldosteronism scheduled for adrenal vein sampling who had given informed consent for participation in the study were included. The study was approved by the local Ethical Committee (2/13 GRANT). The study was conducted in accordance with the Declaration of Helsinki.

The diagnosis of PA was made in the Centre for the Diagnosis and Treatment of Arterial Hypertension in accordance with the current guidelines on the diagnosis and treatment of PA (low plasma renin, high aldosterone, high aldosterone/renin ratio, non-suppressibility of aldosterone production during saline infusion loading tests) (Funder *et al.* 2008, Šomlóová *et al.* 2016). The only allowed antihypertensive medication was verapamil and doxazosin at least 2-3 weeks before the study. Oral potassium supplementation was given, if needed, aiming to correct hypokalemia before all examinations.

Cardiopulmonary exercise stress test – CPX

Exercise stress tests were carried out on a cycle ergometer (Ergoline e-bike, GE Medical Systems, Milwaukee, USA). A combined protocol with two consecutive 3-min constant load steps followed by a ramped increase in work intensity was used. The first step's intensity was set to correspond to 0.5 Watt/kg (i.e. 2.3 metabolic equivalent of task [METs]) and then during the second step, work intensity was increased to 1.0 Watt/kg (i.e. 4.7 METs). When appropriate (e.g. rapid blood pressure rise during the first workload), an intermediate step of 0.75 Watt/kg was inserted. The ramp increase was 5 Watt/10 s, i.e. 30 Watt/min, irrespective of body weight. During the CPX, the following parameters were measured at each step: workload (Watt), systolic blood pressure – SBP (mmHg), diastolic blood pressure – DBP (mmHg), heart rate – HR (beat per minute – bpm), oxygen consumption – VO_2 (ml/kg/min), carbon dioxide output – VCO_2 (ml/min), and RPE – rating of perceived exertion according to Borg (1974). The lower case $_0$ marks baseline data; $_{0.5}$, $_{1.0}$ and $_{peak}$ data at work rate of 0.5 Watt/kg, 1.0 Watt/kg and peak workload, respectively.

BP measurements were performed by an experienced nurse at the beginning of the third minute of each workload, and every odd minute during the ramped increase. BP was measured manually by a standard sphygmomanometer using the auscultatory method. SBP was recorded at the appearance of the Korotkoff phase I sound and DBP at the disappearance or muffling of the Korotkoff sounds (phase IV or V); the preference was at the complete disappearance of the Korotkoff sound, and in the case of uncertainty, diastolic pressure was not noted. HR was measured online from the ECG recording by the cardiological software (GE Cardiosoft V6.51, GE Medical Systems, Milwaukee, USA).

Analysis of expired gas was performed breath-by-breath using Vmax Spectra 29s Cardiopulmonary Exercise Testing Instrument (SensorMedics Corporation, Yorba Linda, Canada). Flow and sensor calibration was performed before each test according to the device manual. The respiratory exchange ratio (RER; VCO_2/VO_2) and metabolic equivalent of tasks (METs; VO_2 /basal oxygen demand [3.5 ml/kg/min]) were calculated from the measured variables.

Markers of cardiopulmonary fitness included VO_{2peak} (mean from the last 30 s of the exercise test)

expressed in ml/kg/min, as a percentage of the national norm ($VO_{2peak}\%$). These data were derived from the specific national data from the international biological programme (Selinger and Bartůněk 1976), as it is widely used in reporting fitness data, where less than 85 % is considered abnormal (Máček and Radvanský 2011).

Laboratory analysis

A blood sample was taken before the CPX and after recovery, i.e. approximately 5-7 min after peak exercise. Plasma renin (PR) and aldosterone (Aldo) were measured by radioimmunoanalysis using commercially available kits (Immunotech; Beckman Coulter Company, Prague, Czech Republic). Serum cortisol levels were measured using the competitive chemiluminiscent immunoassay (ADVIA: Centaur Siemens, Erlangen, Federal Republic of Germany). Interassay coefficient of Variability was 9.5 %.

Ambulatory blood pressure monitoring

Twenty-four-hour ambulatory BP monitoring (ABPM) was performed using an oscillometric device (SpaceLabs 90207 or 90217; SpaceLabs Medical, Redmond, Washington, USA), which was set to measure every 20 min during the day (from 06:00 to 22:00 h) and every 30 min during the night (from 22:00 to 06:00 h). The measurement was performed during a short hospitalisation. The following parameters were measured: SBP, DBP, HR and their standard deviations during the whole period and during the daytime and night-time periods. The suffix $_{24}$, $_{day}$ and $_{night}$ were used respectively.

Echocardiography

A standard protocol was used in all patients, i.e. M-mode, two-dimensional imaging and Doppler flow analyses were recorded in patients, positioned supine in the left lateral decubitus position. When the variable was corrected by body surface area, the suffix “ $_i$ ” was used.

From the parasternal long axis (PLAX), left ventricle (LV) end-diastolic (LVED) and LV end-systolic dimensions (LVES), interventricular septum (IVS), and posterior wall thickness (PWT) were measured in M-mode frozen image according to the recommendations of the American Society of Echocardiography (Lang *et al.* 2005). The relative wall thickness (RWT) was calculated from these data as $2 \times (PWT/LVED)$ and LV mass was estimated using standard build-in software. The

LV mass (LVM) was normalised to body surface area (LVM_i). LV hypertrophy was considered if $LVM_i \geq 125 \text{ g/m}^2$ in men and $LVM_i \geq 100 \text{ g/m}^2$ in women. Left ventricle ejection fraction (LVEF) was calculated as $LVED - LVES/LVED$. LV diastolic function was evaluated from Doppler transmitral flow data and tissue Doppler imaging of medial and lateral mitral annulus movement. Left atrial volume was measured in A4C view and normalised to body surface area (Indra *et al.* 2015).

Statistics

All calculations were performed using SPSS 13.0 statistical software (SPSS Inc. Chicago, IL 60606-6412, USA). Continuous variables were expressed as mean \pm SD and the range was reported where appropriate. A linear regression analysis with multivariate models was used with stepwise variable selection. Before linear regression analysis, Pearson's correlation coefficients between independent and dependent variables were calculated. Peak work rate indexed by body weight, SBP_{peak} , DBP_{peak} , VO_{2peak} and $VO_{2peak}\%$ were chosen as dependent variables *a priori*. Differences between groups were tested using Student's unpaired t-test. The level of significance was set at $p < 0.05$.

Results

A total of 27 patients was included in this study. Basic demographic data are summarised in Table 1. Only one patient had a history of coronary artery disease, four patients had type 2 diabetes (none of them was on insulin therapy), eleven patients had previously been treated for dyslipidaemia, no patient had a pulmonary disease and four patients were on stable (>6 months) substitution therapy for hypothyroidism. There was only one current smoker in our population, nine patients had been ex-smokers for more than ten years before taking part in this study.

Males had higher BMI ($32.8 \pm 3.4 \text{ kg/m}^2$ vs. $25.6 \pm 3.1 \text{ kg/m}^2$, $p < 0.001$) and higher waist circumference (112 ± 9.7 vs. $91 \pm 9.3 \text{ cm}$, $p < 0.001$). Male gender was associated with significantly higher number (4.1 ± 1.1 vs. 2.7 ± 1.5 , $p = 0.009$) and doses of antihypertensive drugs. On the other hand female gender was associated with lower kalemia (3.5 ± 0.3 vs. $3.8 \pm 0.4 \text{ mmol/l}$, $p = 0.03$) despite a similar potassium supplementation.

Table 1. Study population characteristics.

	Mean±SD	Range: min; max
No. patients	27	
Male / female	17/10	N/A
Age (years)	49.9±10.4	33.2; 69.8
Weight (kg)	93.2±22.7	58; 142
Waist circumference – WC (cm)	104.7±13.6	77; 128
BMI	30.2±4.8	21.8; 37.4
Hypertension duration (years)	10.1±6.7	0.5; 27.0
Number of hypertensive drugs before verapamil/doxazosin switch	3.6±1.4	1; 6
Verapamil dose (mg)	289.6±166.5	0; 480
Doxazosin dose (mg)	5.4±4.8	0; 16
Kalium chloratum dose (g)	5.2±3.5	0; 12
Kalemia (mmol/l)	3.7±0.3	2.9; 4.3
Number of patients indicated to adrenalectomy	18	N/A
Number of patients indicated to aldosterone antagonist therapy	9	N/A

Table 2. Cardiopulmonary exercise stress test data.

	Baseline	Exercise			Peak	Recovery		
		0.5 W/kg	0.75 W/kg	1.0 W/kg		1 min	3 min	5 min
N		27	4	25	27	27	27	27
Workload (Watt)	0	46±12	78±18	92±23	181±60	N/A	N/A	N/A
SBP (mm Hg)	139±27	153±27	213±21	171±28	195±26	172±33	156±31	139±29
DBP (mm Hg)	87±11	88±12	101±3	91±11	95±12	82±14	79±13	79±14
HR (bpm)	88±18	108±16	122±8	129±18	152±25	133±23	107±20	100±19
VO ₂ (ml/kg/min)	4.2±0.9	11.7±0.84	15.1±1.6	18.2±1.2	25.4±6.0	N/A	N/A	N/A
METs	1.2±0.3	3.3±0.2	4.3±0.5	5.2±0.3	7.3±1.7	N/A	N/A	N/A
RER	0.92±0.12	0.87±0.07	0.96±0.03	1.01±0.08	1.16±0.1	N/A	N/A	N/A
RPE	N/A	9.0±1.7	12.6±1.1	12.7±1.5	15.8±1.7	N/A	N/A	N/A

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; VO₂, oxygen consumption; METs, metabolic equivalent of task, RER – respiratory exchange ratio; RPE, rating of perceived exertion according to Borg; N/A, not applicable.

The data from the CPX are reported in Table 2. The CPX test length was 8:52±1:24 min:s. VO_{2peak} was 25.4±6.0 ml/kg/min which corresponds to VO_{2peak}% of 80.8±18.9 %. Men attained non-significantly lower VO_{2peak} (24.8±7.1 vs. 26.4±0.6 ml/kg/min; p=0.5), whereas VO_{2peak}% was significantly lower (73.9±20.5 vs. 92.6±6.4 %, p=0.01).

Four patients underwent the step of 0.75 Watt/kg intensity, and only two continued further. The test was terminated prematurely before patient's maximum in three patients, due to excessive blood pressure rise (SBP_{peak} were 240; 235; 235 mmHg and DBP_{peak} were

100; 100; 100 mmHg), which was very near the patients' metabolic maximum as seen by the RER 1.14; 1.03; 0.99.

Ambulatory blood pressure monitoring

SBP₂₄ was 148±13 mmHg, DBP₂₄ 90±9 mmHg and HR₂₄ 69±10 bpm. SBP_{day} was 151±13 mmHg, DBP_{day} was 91±12 mmHg and HR_{day} was 72±11 bpm. SBP_{night} was 139±15 mmHg, DBP_{night} was 84±9 mmHg and HR_{night} was 61±10 bpm.

Hormonal changes during CPX

After CPX all PR, Aldo and Cortisol increased

in the majority of patients, their changes are summarised in Table 3. PR and Aldo increased in all, except in three patients with unilateral adenomas.

Table 3. Hormonal changes before and after cardiopulmonary exercise testing.

	Before CPX	After CPX	P value
PR (pg/ml)	4.3±3.5	5.3±4.0	0.005
Aldo (ng/dl)	30.5±19.0	50.8±37.1	0.001
Aldo/PR (ng/dl/pg/ml)	14.4±20.1	16.4±23.3	0.69
Cortisol (nmol/l)	360.0±87.0	491.5±80.1	0.0007

PR, plasma renin; Aldo, plasma aldosterone; CPX, cardiopulmonary exercise test.

Linear regression analysis

Pearson's correlation coefficients were calculated to select appropriate independent variables for the stepwise linear regression analysis; the results of the analysis are summarised in Table 4. As independent variables for the linear regression analysis, age, verapamil and doxazosin dose, BMI, waist circumference (WC), SBP₀, DBP₀ and HR₀, ABPM data, kalemia, LVED_i,

LVM_i, LVEF, LAV_i were chosen.

Linear regression analysis showed that SBP_{peak} depends primarily on DBP₀ (p=0.001), on kalemia (p=0.006) and HR₀ (p=0.014):

$$SBP_{peak} = 54.5 + 1.1 \times DBP_0 + 26.8 \times Kalemia - 0.8 \times HR_0$$

DBP_{peak} depends primarily on DBP₀ (p = 0.002) and on BMI (p=0.033):

$$DBP_{peak} = 69.2 + 0.6 \times DBP_0 - 1.0 \times BMI$$

Linear regression analysis showed that Workload_{peak} depends primarily on doxazosin dose (p=0.001), then on HR_{day} (p=0.002) and on WC (p=0.032).

$$WorkLoad_{peak} = 5.0 - 0.2 \times Doxazosin-dose - 0.1 \times HR_{day} + 0.02 \times WC$$

Linear regression analysis showed that VO_{2peak} depends on doxazosin dose (p=0.001) and kalemia (p=0.02).

$$VO_{2peak} = 4.2 - 1.0 \times Doxazosin-dose + 7.6 \times Kalemia$$

Linear regression analysis showed that VO_{2peak}% depends only on doxazosin dose (p=0.003)

$$VO_{2peak}\% = 98.1 - 3.0 \times Doxazosin-dose$$

Table 4. Pearson's correlation coefficients (only significant results are shown).

	Peak work intensity	SBP _{peak}	DBP _{peak}	VO _{2peak}	VO _{2peak} %
Age	-0.540**			-0.499**	
Doxazosin dose	-0.685**			-0.585**	-0.626**
Waist circumference	0.420*				-0.391*
BMI			-0.393*		
SBP ₀		0.747**			
DBP ₀		0.729**	0.413*		
SBP ₂₄				-0.520*	-0.570**
SBP _{day}				-0.456*	-0.532**
DBP _{day}				0.405*	
SBP _{night}	-0.450*			-0.615**	-0.623**
LVM _i	-0.401*				-0.457*

SBP, systolic blood pressure; DBP, diastolic blood pressure; LVM_i, left ventricle mass index; VO₂, oxygen consumption, * for p<0.05; ** for p<0.01.

Differences according to doxazosin dosing

As Doxazosin dose was the most significant determinant of VO_{2peak} , the study population was divided according to doxazosin dose: DX_{low} group with doses ≤ 4 mg per day and DX_{high} with doses ≥ 6 mg per day. The patients in the DX_{low} group were younger (45 ± 9 vs. 56 ± 8 years; $p=0.0027$), with shorter hypertension duration (7.4 ± 6.2 vs. 13.4 ± 5.8 ; $p=0.021$), with lower BMI (27.8 ± 4.1 vs. 33.1 ± 4.1 ; $p=0.0028$) and lower WC (98 ± 12 vs. 113 ± 11 cm; $p=0.002$). Besides doxazosin, they used a lower dose of verapamil (201 ± 147 vs. 400 ± 118 mg; $p < 0.001$), but with a comparable dose of potassium supplementation and with comparable kalemia. Before the switch to doxazosin and/or verapamil therapy, the patients in DX_{low} had a lower number of hypertensive drugs (2.7 ± 1.1 vs. 4.7 ± 0.9 ; $p < 0.0001$). They had lower SBP during all test phases, namely: exercise, recovery and ABPM. They reached higher peak workload (2.3 ± 0.6 vs. 1.6 ± 0.5 Watt/kg; $p=0.005$), and a trend toward higher VO_{2peak} (27.4 ± 5.2 vs. 23.0 vs. 6.3 ml/kg/min; $p=0.055$) and $VO_{2peak\%}$ (87 ± 15 vs. 73 ± 21 ; $p=0.07$) was observed. From the echocardiographic study, patients in the DX_{low} group had higher LVEDi (26.7 ± 3.5 vs. 23.2 ± 2.8 ; $p=0.012$) but not LVED (51 ± 6 vs. 52 ± 9 ; NS).

In the DX_{low} group, nine of the fifteen patients had normal left ventricular diastolic function, whereas only two of the twelve in the DX_{high} had normal left ventricular diastolic function. All other patients in both groups had impaired relaxation.

Discussion

In our study, lower exercise capacity in patients with PA compared to the general population was found, mainly depending on kalemia and doses of antihypertensive medication indicating the severity of hypertension.

VO_{2peak} depended on kalemia. Hypokalemia decreases potassium channel conductance hyperpolarising skeletal muscle cells and impairs their ability to develop the depolarisation necessary for muscle contraction (Cheng *et al.* 2013). This activity-dependent process may contribute to weakness, easy fatigability and paralysis developing with hypokalemia after exercise (Huang *et al.* 1996, Krishnan *et al.* 2005, Wen *et al.* 2013). Symptomatic hypokalemia is also associated with microscopic evidence of myocytes' swelling (Ishikawa *et al.* 1985). In severe hypokalemia (blood potassium levels < 2 mmol/l), rhabdomyolysis with

microscopic signs of diffuse muscle necrosis was observed (Ishikawa *et al.* 1985).

The results highlight the need for the maximum effort to supplement potassium depletion in these patients. Despite great attention being paid in our study to potassium supplementation, kalemia remained at the lower limit of normal values and, in some patients, kalemia was below the lower limit despite high supplementary doses.

The gender differences in exercise capacity may be explained by the anthropometric parameters. BMI and WC were both higher in men, and there is good evidence that obesity is inversely related to exercise capacity (Wasserman 2012).

Higher doxazosin dose could be a marker of more severe and long-standing hypertension (maybe also essential) and impaired diastolic function (Victor 2015), which is in agreement with our finding that patients in the DX_{high} group had higher SBP and more often echocardiographic signs of diastolic dysfunction. Diastolic dysfunction increases preload and higher SBP afterload. Both the higher preload and higher afterload increase the mechanical work performed by the heart and heart oxygen demand (Wasserman 2012), thus limiting maximum cardiac output and, due to coupling of ventilation, cardiac output and muscle oxygen uptake, also peak oxygen consumption (Wasserman 2012).

Moreover, patients in DX_{high} were also older and with higher BMI. With increasing age the VO_{2peak} decreases but $VO_{2peak\%}$ should remain unchanged. In the general population, obesity is negatively related to VO_{2peak} (Hansen *et al.* 1984). Age and obesity can both contribute to diastolic dysfunction (Zile and Little 2015). Patients on a higher doxazosin dose also had a higher verapamil dose. Verapamil has a negative chronotropic effect on the HR (Keteyian 2013) and cardiac output depends almost exclusively on HR at oxygen consumption above 60 % VO_{2peak} , thus HR is the dominant determinant of VO_2 in patients without coronary artery disease (McArdle *et al.* 2010).

Exercise blood pressure depended on resting BP, which is consistent with the finding of other studies, where the exaggerated blood pressure response remained non-significant after adjustment to resting blood pressure (Filipovsky *et al.* 1992). This finding is not surprising, as it is known that the set-point for blood pressure regulation is set higher in patients with long-standing hypertension (Albaghdadi 2007, Brands 2012). In our population of patients with PA, BP increased from

already elevated SBP₀ to 1.0 Watt/kg by a mean of 32 mmHg, which is slightly higher than expected (Tuka *et al.* 2015).

Our data suggest that the exercise stress test can also be safely performed on patients with PA. The test was stopped prematurely only in the case of three patients for safety reasons concerning high blood pressure with values approaching the indication to stop the stress test (Gibbons *et al.* 1997). Exercise testing was also performed in patients with resistant hypertension (Ukena *et al.* 2011).

Our study had some limitations. The most important one is that we could not include a control group. We were not able to find matched patients with essential hypertension, with a similar degree of hypertension to the patients with PA, who were willing to undergo exercise testing. The second limitation is the lack of data on nutritional status and previous physical activity in our patients, both potentially affecting exercise tolerance. Nevertheless from the anthropometric data

(mean BMI corresponding to first degree obesity) the patients did not follow a special diet. The volume and type of previous physical activity was not known, nevertheless none of the patients was an athlete.

Conclusion

Patients with PA have lower cardiopulmonary fitness which depends inversely on the severity of hypertension and kalemia. Exercise testing in subjects with PA is safe and is not associated with excessive BP increase.

Conflict of Interest

There is no conflict of interest.

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