The effect of adrenalectomy on exercise response of the renin-angiotensin-aldosterone system and exercise tolerance in primary aldosteronism

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Summary

Primary aldosteronism (PA) is associated with objectively measured lower physical fitness and blunted response of the renin-angiotensin-aldosterone system to exercise. The purpose of this pilot study was to objectively measure exercise response of the renin-angiotensin-aldosterone system and cardiopulmonary fitness changes after laparoscopic adrenalectomy (ADE) in patients with unilateral PA. We examined a total of 14 patients with confirmed PA before and after ADE, by means of spiroergometry and hormonal evaluation. As expected, after adrenalectomy basal aldosterone (Aldo) levels before exercise decreased significantly, with a concomitant increase in plasma renin (PR). The increase in Aldo (285.9 ± 171.3 to 434.1 ± 278.2ng / l; $p = 0.02$) and blunted increase in PR (7.1 ± 0.4 to 8.9 ± 10.4 pg / ml; NS) post-exercise before ADE became significant after ADE: Aldo post-ADE (46.8 ± 18.8 to 106.5 ± 68.1; $p < 0.0001$) and PR post-ADE (20.1 ± 14.5 to 33.9 ± 30.7; $p = 0.014$). After adrenalectomy, the patients had a non-significant increase in peak workload and VO_{2peak}. We found normalisation of the renin-angiotensin-aldosterone system response to exercise with little changes in cardiopulmonary fitness six months after ADE.

Key words:

Primary hyperaldosteronism; unilateral adrenalectomy; physical fitness; exercise blood pressure; exercise stress test

Introduction

Primary aldosteronism (PA) is the most common form of secondary hypertension affecting at least 4 % of patients with moderate to severe hypertension.(Funder et al. 2016) Low levels of serum potassium are found in the majority of patients with PA (Somloova et al. 2016). Hypokalaemia influences muscle function, which leads to easy fatigability and muscle weakness (Gennari 1998). Patients with PA also have lower quality of life, especially in the domains of physical functioning, vitality, and general health (Sukor et al. 2010). PA is associated with objectively measured lower physical fitness, which is inversely dependent on kalaemia and the severity of hypertension (Tuka et al. 2016). Furthermore, the response of the renin-angiotensin-aldosterone system is blunted during maximal exercise (Tuka et al. 2016).

Unilateral adrenalectomy (ADE) is the therapy of choice in patients with PA with unilateral aldosterone overproduction (Stowasser 2014). After ADE, many patients are cured of hypertension and the remaining have a significant decrease in antihypertensive medication (Letavernier et al. 2008, Stowasser 2014). Furthermore, already three months post-surgery, their quality of life (in both physical and psychological domains) improves, approaching that of the general population (Sukor et al. 2010).

The purpose of this pilot study was to objectively measure exercise response of the renin-angiotensin-aldosterone system and cardiopulmonary fitness changes after laparoscopic adrenalectomy in patients with unilateral PA. We hypothesised that ADE through hormonal and potassium level normalisation and blood pressure (BP) decrease will lead to improved physical fitness.

Patients and Methods

Study population

We examined a total of 18 patients with confirmed PA, who were indicated for ADE after adrenal vein sampling performed between May 2013 and October 2014. All patients were scheduled for a cardiopulmonary exercise stress test (CPX) and ambulatory blood pressure monitoring after adrenal vein sampling (Pre-ADE) and 6 months after ADE (Post-ADE). Of the 18 patients who underwent ADE, 15 arrived for the second CPX. In one patient, significant post-exercise hypotension occurred and was excluded from analysis. Data from the remaining 14 patients were analysed. Four patients were treated with dyslipidaemia, one patient had Type 2 diabetes and two patients were on stable (> 6 months) substitution therapy for hypothyroidism. There was only one current smoker in our population; seven patients had been ex-smokers for more than ten years before taking part in this study. The patients were advised not to exercise for the first four to six weeks after ADE. Thereafter, they were advised to resume their normal daily activities without special advice on physical activity.

All patients gave informed consent. The study was approved by the local Ethical Committee (2/13 GRANT) and 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-supressibility of aldosterone production during saline infusion loading tests)(Funder et al. 2016, Somloova et al. 2016). The only allowed antihypertensive medication at study entry was verapamil and doxazosin at least 2-3 weeks before the study. Oral potassium supplementation was given, if needed, aiming to correct hypokalaemia before all examinations.

Cardiopulmonary exercise stress test

Exercise stress tests were carried out on a cycle ergometer (Ergoline e-bike, GE Medical Systems, Milwaukee, USA) with a combined protocol, with two consecutive 3-min constant load steps (0.5 Watt / kg and 1.0 Watt / kg), followed by a ramped increase in work intensity. During the CPX, the following parameters were measured at each step as described in our previous publication (Tuka et al. 2016): 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.(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.

Laboratory analysis

A blood sample was taken before the CPX and after recovery, i.e. approximately 5-7 minutes 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 following parameters

were measured: SBP, DBP, HR and their standard deviations during the whole period and during the daytime and night-time periods. The suffixes $_{24}$, $_{day}$ and $_{night}$ were used respectively.

Statistics

All calculations were performed using StatSoft, Inc. (2013). STATISTICA (data analysis software system), version 12. Continuous variables were expressed as mean $\pm$ SD. The hormonal changes were tested, using Student's paired t-test. The differences between data Pre-ADE and Post-ADE were tested, using Student's paired t-test. The level of significance was set at $p < 0.05$.

Results

After ADE, 10 patients did not use any antihypertensive drugs, three patients still used verapamil at a dose of 240 mg once daily (one with concomitant use of telmisartan 80 mg once daily), and one patient still used doxazosin 4 mg daily with concomitant use of perindopril 4 mg once daily. After ADE, no patient required potassium supplementation and all had normal kalaemia (Table 1). As expected, blood pressures dropped. The blood pressures obtained during ABPM are summarised in Table 2.

As expected, after ADE basal Aldo before exercise decreased significantly with a concomitant increase in PR. The blunted increase in both Aldo and PR post-exercise before ADE became significant after ADE (Table 3).

After ADE, the patients had a non-significant increase in peak workload and VO_{2peak}. The $VO_{2peak}SD$ increased non-significantly (-0.78 ± 1.1 vs. -0.68 ± 1.3 ml/kg/min, p = 0.8) and $VO_{2peak}\%$ also increased non-significantly (89 ± 15 vs. 91 ± 17 %, p = 0.7). The length of the test was non-significantly longer after ADE (9:04 ± 1:08 vs. 9:30 ± 1:18 min, p = 0.2). The biggest changes, although non-significant, were observed in younger patients (Figure 1). We observed significantly higher heart rate at baseline, peak exercise and recovery period after ADE. The haemodynamic response during CPX is summarised in Table 4.

Discussion

To our knowledge, this is the first study dealing with changes of cardiopulmonary fitness induced by therapy of PA (unilateral ADE in patients with PA). We observed normalisation of the renin-angiotensin-aldosterone system, kalaemia and BP decrease. Cardiopulmonary fitness increased only non-significantly and mostly in younger patients.

Before ADE, Aldo increased significantly, but from elevated basal values after dynamic exercise, whereas the basally suppressed PR did not increase significantly. After ADE, Aldo and PR increased from normal basal values, as would be expected in healthy untrained men and women (Kinugawa et al. 1997, Borer 2013). This shows a restitution of normal functioning of the renin-angiotensin-aldosterone system during exercise.

As observed earlier, the quality of life in all domains, also encompassing physical performance, improves as early as 3 months after ADE (Sukor et al. 2010). In our cohort, the cardiopulmonary fitness parameters did not increase significantly at 6 months, but there was a trend of longer test duration after ADE. There could be several reasons. The 6 months are too short a period of time to improve the long influence of aldosterone and hypokalaemia on skeletal muscles. Furthermore, after ADE patients are advised not to exercise for the first four to six weeks. On the other hand, after exercise training, changes in cardiopulmonary fitness parameters can be observed as early as 3 months after initiation of training (McArdle et al. 2010).

The physical performance and easy fatigability in patients with PA could rather be linked to muscular endurance than acute cardiovascular performance. This could explain the improvement of quality of life in the study by Sukor et al. and non-significant changes in the cardiopulmonary exercise test (Sukor et al. 2010). A more sensitive test could be the use of a test with pre-set (75-80 % VO_{2peak}) continuous submaximal intensity and a comparison of endurance time of the exercise patients would perform (Palange et al. 2007). This approach

was shown to be superior in e.g. patients with chronic obstructive pulmonary disease after oxitropium bromide initiation, where traditional measures of exercise performance (maximal workload, VO_{2max}) increased by only 5 %, whereas endurance time increased by 19 % (Oga et al. 2000).

The final possibility is the size of the cohort which is relatively small, which could affect the potential to produce statistically significant changes in VO_{2peak}. This explanation is less probable, because half of the patients in the cohort improved and half decreased their VO_{2peak}.

A potential confounder in our cohort is the use of verapamil during the exercise test pre-ADE in most patients, and its use only by three patients in the exercise test post-ADE, which explains the higher HR post-ADE. Verapamil was shown to improve left ventricular filling pressures and to improve exercise performance in elderly hypertensive and normotensive individuals (Petrella et al. 1994). This could be partially explained by reduced ventriculo-vascular stiffening. After verapamil intravenous injection, elderly volunteers performed better than after saline injection. After verapamil, exercise duration before anaerobic threshold and total exercise duration increased without no change in VO_{2max} (Chen et al. 1999).

The strength of the study is the uniform cohort of patients with the objectively established diagnosis of unilaterality of PA in whom ADE led to a significant decrease of BP and normalisation of hypokalaemia. On the other hand, the limitation of the study is the lack of a control group.

In conclusion, we found normalisation of the renin-angiotensin-aldosterone system response to exercise with little changes in cardiopulmonary fitness six months after ADE. For future investigations of cardiopulmonary fitness in patients with PA, endurance tests with a concomitant quality of life measurement would be more appropriate. Future research should

also study the effect of medical therapy of PA on cardiopulmonary fitness and the effect of exercise prescription.

Acknowledgements

Conflict of interest

The authors declare that there is no conflict of interests.

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Table 1. Study population characteristics before and 6 months after adrenalectomy

	Pre – ADE	Post – ADE	p – value
No. patients	14	14	
Male / female	7 / 7	N/A	
Age (years)	48 ± 10	N/A	
Weight (kg)	90.9 ± 27.0	88.9 ± 23.5	NS
Waist circumference (cm)	104 ± 16	104 ± 17	NS
BMI	29.7 ± 5,6	29.3 ± 4.9	NS
No. patients on verapamil	14	3	0.008
No. patients on doxazosin	14	1	0.0018
Kalium chloratum dose (g)	5.7 ± 3.9	0	0.000094
Kalemia (mmol / l)	3.7 ± 0.4	4.5 ± 0.2	0.000021

Pre-ADE – before adrenalectomy; Post-ADE – 6 months after adrenalectomy, NS – non-significant

Table 2. Ambulatory blood pressure monitoring data before and 6 months after adrenalectomy

		Pre-ADE	**Post-ADE**	p – value
All day	SBP (mmHg)	145 ± 9	128 ± 11	0.002
	DBP (mmHg)	90 ± 7	81 ± 9	0.026
	HR (bpm)	64 ± 9	70 ± 9	0.13
Day time	SBP (mmHg)	149 ± 11	131 ± 11	0.004
	DBP (mmHg)	93 ± 6	84 ± 9	0.03
	HR (bpm)	67 ± 9	73 ± 11	0.08
Night time	SBP (mmHg)	134 ± 7	120 ± 11	0.003
	DBP (mmHg)	83 ± 7	74 ± 10	0.03
	HR (bpm)	58 ± 9	62 ± 7	0.22

Pre-ADE – before adrenalectomy; Post-ADE – 6 months after adrenalectomy

Table 3. Hormonal changes before and after cardiopulmonary exercise testing before and 6 months after adrenalectomy

		Pre CPX	Post CPX	P value Pre-CPX vs. post-CPX
PR (pg / ml)	Pre-ADE	7.1 ± 0,4	8.9 ± 10.4	NS
	Post-ADE	20.1 ± 14.5**	33.9 ± 30.7**	0.014
Aldo (ng / l)	Pre-ADE	285.9 ± 171.3	434.1 ± 278.2	0.02
	Post-ADE	46.8 ± 18.8***	106.5 ± 68.1**	< 0.0001
Aldo /PR (ng / dl)	Pre-ADE	9.9 ± 11.8	10.9 ± 12.7	NS
	Post-ADE	0.3 ± 0.2*	0.5 ± 0.4*	0.001
Cortisol (nmol / l)	Pre-ADE	329 ± 93	507 ± 74	0.03
	Post-ADE	366 ± 53	474 ± 89	< 0.001

PR, plasma renin; Aldo, plasma aldosterone; CPX, cardiopulmonary exercise test; Pre-ADE – before adrenalectomy; Post-ADE – 6 months after adrenalectomy, NS – non-significant

For * < 0.05; ** < 0.01; *** < 0.001 comparing Pre-ADE and Post-ADE

Table 4. Cardiopulmonary exercise stress test data before and 6 months after adrenalectomy

		Baseline	Exercise			Recovery		
			0.5 W / kg	1.0 W / kg	Peak	1 min	3 min	5 min
Workload (Watt)	Pre-ADE	N/A	45 ± 14	90 ± 27	189 ± 57	N/A	N/A	N/A
	Post-ADE	N/A	44 ± 11	88 ± 24	200 ± 54	N/A	N/A	N/A
SBP (mmHg)	Pre-ADE	138 ± 21	148 ± 23	170 ± 23	192 ± 27	172 ± 38	154 ± 34	135 ± 27
	Post-ADE	132 ± 13	146 ± 17	164 ± 24	197 ± 34	173 ± 35	153 ± 27	131 ± 17
DBP (mmHg)	Pre-ADE	86 ± 10	88 ± 12	91 ± 10	96 ± 13	82 ± 15	76 ± 13	76 ± 12
	Post-ADE	87 ± 7	92 ± 7	94 ± 7	105 ± 9	91 ± 9	87 ± 5*	85 ± 7
HR (bpm)	Pre-ADE	81 ± 14	101 ± 13	124 ± 19	151 ± 24	126 ± 23	98 ± 16	93 ± 16
	Post-ADE	87 ± 18*	108 ± 16	129 ± 20	166 ± 14***	141 ± 14**	110 ± 18***	99 ± 18
VO$_2$ (ml/kg/min)	Pre-ADE	N/A	11.9 ± 0.9	18.5 ± 1.1	27.7 ± 4.8	N/A	N/A	N/A
	Post-ADE	N/A	11.8 ± 1.6	17.4 ± 1.9	29.0 ± 5.3	N/A	N/A	N/A
RPE	Pre-ADE	N/A	8.3 ± 1.4	12.5 ± 1.2	16.1 ± 1.4	N/A	N/A	N/A
	Post-ADE	N/A	8.5 ± 1.8	12.1 ± 1.2	16.4 ± 2.1	N/A	N/A	N/A

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; VO_2, oxygen consumption; METs, metabolic equivalent of task, RER – respiratory exchange ratio; RPE, rating of perceived exertion according to Borg; Pre-ADE – before adrenalectomy; Post-ADE – 6 months after adrenalectomy

N/A, not applicable
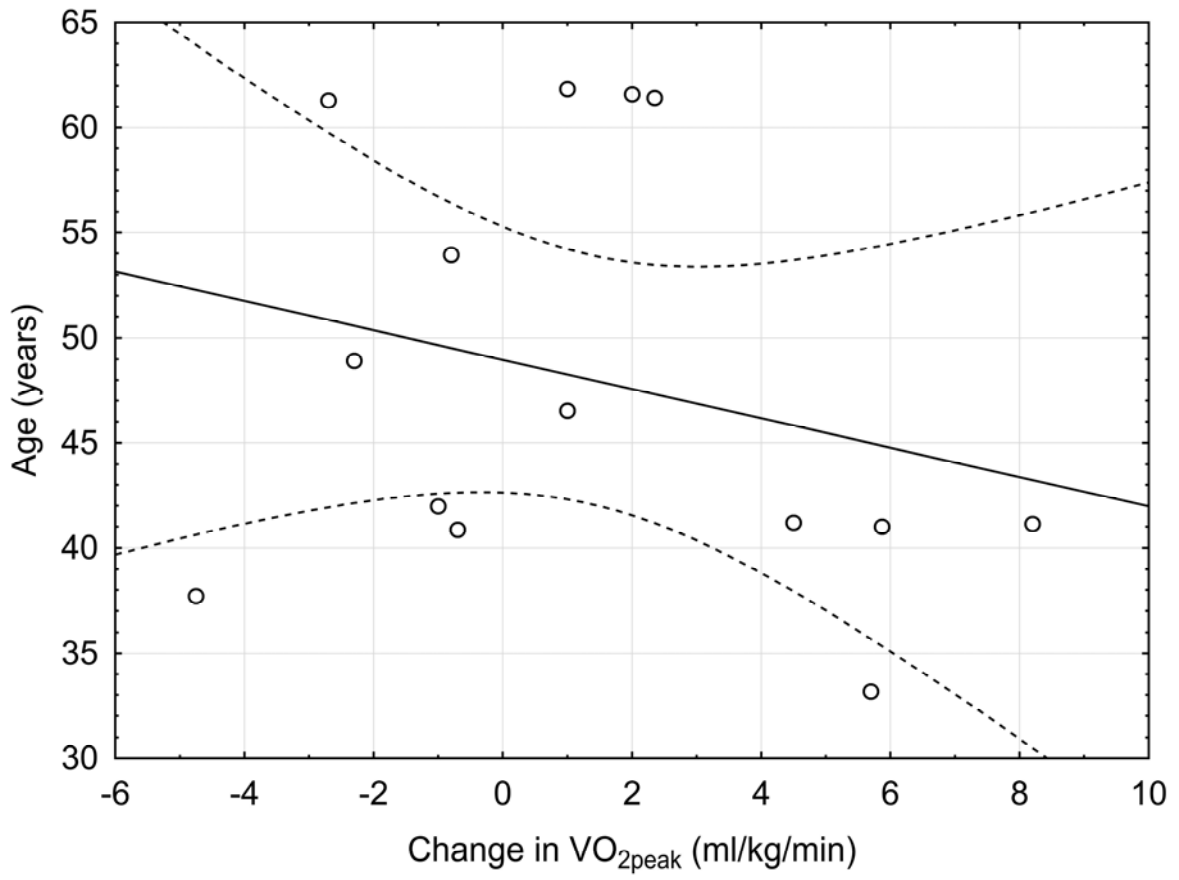
* < 0.05; ** < 0.01; *** < 0.001

Figure 1. The correlation of the change in peak oxygen consumption (VO_{2peak}) and patients' age.