Inflammatory markers in primary aldosteronism

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Short title: Differences in main types of primary aldosteronism

Summary

Primary aldosteronism (PA) is the most common cause of endocrine hypertension with a high frequency of cardiovascular complications. The unfavorable cardiometabolic profile may be due to aldosterone-mediated activation of inflammatory cells, circulatory cytokines and activation of collagen synthesis in the vessel wall. Aim of our study was to evaluate differences in the levels of hsCRP, IL-6, TNF-α and N-terminal propeptide of collagen I (PINP) in patients with PA and essential hypertension (EH) as a control group, and between the subtypes of PA (aldosterone producing adenoma-APA, idiopathic hyperaldosteronism-IHA). We studied 28 patients with PA (IHA-10 patients, APA-12 patients, 6 unclassified) and 28 matched patients with EH. There were no differences in the levels of inflammatory markers between the followed groups [EH vs. PA: TNF-α (5.09[3.68-6.32] vs. 4.84[3.62-6.50]pg/ml), IL-6 (0.94[0.70-1.13] vs. 0.97[0.71-1.28]pg/ml), hsCRP (0.53[0.25-1.54] vs. 0.37[0.31-0.61]mg/l), leukocytes (6.35±1.42 vs. 5.97±1.29 10^9l); APA vs. IHA: TNF-α (4.54[3.62-7.03] vs. 5.19[4.23-5.27] pg/ml), IL-6 (0.96[0.63-1.21] vs. 0.90[0.65-1.06]pg/ml), hsCRP (0.34[0.29-0.47] vs. 0.75[0.36-1.11]mg/l), leukocytes (6.37±1.41 vs. 5.71±1.21 10^9l)]. Significant differences in the levels of PINP between PA and EH group were observed (35.18[28.46-41.16] vs. 45.21[36.95-62.81]ug/l, $p \leq 0.003$). No differences in inflammatory markers were observed between the followed groups, we confirmed higher levels of PINP in patients with PA.

Keywords: primary aldosteronism, TNF-α, IL-6, hsCRP, PINP

Introduction

Primary aldosteronism (PA) characterized by autonomous overproduction of aldosterone is the most

common cause of endocrine hypertension with a high frequency of cardiovascular complications. The prevalence PA in the non-selected hypertensive population is around 5-13% (Young, 2007; Hannemann and Wallaschofski, 2012) and in a preselected population of patients with severe and resistant hypertension around 20% (Calhoun et al., 2002; Štrauch et al., 2003). The main forms of PA are idiopathic aldosteronism (IHA) caused by bilateral adrenal hyperplasia and unilateral aldosterone producing adenoma (APA). Other forms of PA are less common, and include unilateral hyperplasia and rare familial aldosteronism type I, II and III. Recent data shows that patients with PA have a significantly higher rate of cardiovascular risk than patients with essential hypertension (EH) (Catena et al., 2008). There is an evidence of more frequent left ventricular hypertrophy (Rossi et al., 1996), stroke, atrial fibrillation, myocardial infarction (Milliez et al., 2005) and metabolic syndrome (Fallo et al., 2006) in patients with PA. They have also a higher urinary albumin excretion (Rossi et al., 2006), increased intima-media thickness of the common carotid artery (Holaj et al., 2007) and a higher aortic wall stiffness measured by PWV (Strauch et al., 2006). Specific treatment with adrenalectomy in patients with APA might reverse these changes (Strauch et al., 2008). The unfavorable cardio-metabolic profile in subjects with PA may account for a role of aldosterone that goes beyond its known hypertensive effect (Iacobellis et al., 2010). It might be due to activated inflammatory cells and circulatory cytokines (Haluzík et al., 2002; Carvajal et al., 2009; Staermose et al., 2009; Iacobellis et al., 2010) and due to activation of collagen synthesis in the vessels. It has been reported, that patients with EH have an increased circulating levels of immunoglobulins, autoantibodies, decreased numbers and altered functions of T-lymphocytes (Peeters et al., 2001). An altered profile of pro- and anti-inflammatory cytokines, such as TNF-α and IL-6, and activation of monocyte can be involved in the pathogenesis of hypertension and in changes of the arterial wall in hypertension (Peeters et al., 2001; Harrison et al., 2010). However, the effect of aldosterone overproduction on the inflammatory profile and collagen synthesis in primary aldosteronism is not clearly established. In patients with primary aldosteronism a higher level of PINP was observed but no difference in ultrasensitive CRP was found and no investigation was made to evaluate eventual subgroup differences in inflammatory markers between aldosterone producing adenoma and idiopathic hyperaldosteronism (Stehr et al., 2010). In our recent study we investigated the hypothesis, that in primary aldosteronism an immunostimulatory state is present. Because there are metabolic differences between APA and IHA(Somlóová et al., 2010) we assume, that there might be differences in inflammatory markers between aldosterone producing adenoma and idiopathic hyperaldosteronism. Aim of our study was to evaluate potential differences in the levels of hsCRP, IL-6, TNF-α and the N-terminal pro-peptide of collagen I, marker of collagen synthesis, in patients with PA and EH as a control group and between the most common subtypes of

primary aldosteronism- APA vs. IHA.

Methods

Study population

We studied 28 patients with PA and 28 patients with EH matched by age, blood pressure, duration of hypertension and the prevalence of the metabolic syndrome. Within the group of PA we further analyzed the subgroup of 10 patients with IHA and 12 patients with APA, 6 patients remained unclassified. Subjects were recruited from consecutive patients referred to our Hypertension center in order to exclude secondary hypertension. Patients with renal failure were not included into this study, and all the patients were on a normal sodium/potassium diet with no caloric restrictions.

Clinical evaluation

To standardize the treatment and to eliminate the interferences of anti-hypertensive drugs with the renin-angiotensin-aldosterone system, the previous anti-hypertensive therapy was withdrawn in all patients at least two weeks (in case of spironolactone at least 4 weeks) before the investigation in our center and was switched to an alpha-blocker (doxazosin) and a slow-releasing calcium channel blocker (verapamil). Patients with hypokalemia have continued with oral potassium supplementation. The suspicion of PA was based on the findings of aldosterone renin ratio (ARR) > 30 (ng/dl)/(ng/ml/h) or 5.7 (ng/dl)/(ng/l) and plasma aldosterone >15 ng/dl when measured after two-hour upright position. The diagnosis of PA was confirmed by the lack of aldosterone suppression (<7ng/dl) following an intravenous saline load (2L of 0.9% saline infused over 4 hours). Differential diagnosis of PA forms (IHA and APA) was supported by a computed tomography scan and by a selective adrenal vein sampling (AVS). In addition, the diagnosis of APA was confirmed when successful laparoscopic adrenalectomy was associated with normalization of plasma renin activity and plasma aldosterone levels, and by histological verification. The diagnosis of IHA was based on bilateral aldosterone overproduction assessed by AVS procedure. We performed AVS without ACTH stimulation, selectivity was defined as adrenal vein/inferior vena cava cortisol gradient >3 and lateralization was considered to be present when the aldosterone/cortisol ratio at one side was 3 to 4-times greater than that in the contralateral vein.

Laboratory methods

All hormonal tests were performed by radioimmunoanalysis using commercially available kits in the Institutional Central Laboratory. All other biochemical parameters were analyzed using multianalyzers

in the Institutional Central Laboratory. IL-6 was measured with ELISA (Human sIL-6 Instant ELISA CE-IVD, e Bioscience, Multiscan Ascent), hsCRP was measured with ELISA (Human C reactive protein Instant ELISA CE-IVD, e Bioscience, Multiscan Ascent), TNF-α was measured with ELISA (TNF-alfa-EASIA, DIA source, Multiscan Ascent). The serum concentration of intact PINP was measured by a radioimmunoassay (Procollagen Intact PINP, Orion Diagnostica, Espoo, Finland). The within-run imprecision for the PINP was below 5%, and the between-run imprecision was less than 7%. The normal range for serum PINP is 19.3-56.4 μg/l.

Blood pressure measurement

Clinical blood pressure (BP) values were obtained using a validated oscillometric sphygmomanometer (Dinamap, Critikon, Tampa, FL, USA). Three measurements of blood pressure were obtained in the sitting position after a five minute rest period. Final office blood pressure was calculated as average from the second and third blood pressure readings. The 24-hour ambulatory blood pressure monitoring was performed during hospitalization using an oscillometric device (SpaceLabs 90207; SpaceLabs Medical, Redmond, WA, USA).

Statistical methods

The statistical analysis was performed by STATISTICA software vers.12 (Statsoft Inc., Tulsa, OK, USA). Data are expressed depending on the normal/non-normal distribution (Shapiro–Wilks W-test) as means ± standard deviations or median (interquartile range, 25th-75th percentile). Between-group comparisons were performed by two-tailed t-test for independent samples. The Kruskal–Wallis ANOVA test and Mann–Whitney U test was used for non-normally distributed variables. Pearson's correlation analysis and multiple regression analysis (stepwise forward method) were applied to assess the relationship among inflammatory markers and PINP and clinical/laboratory parameters (variables which significantly correlated in Pearson's correlation analysis entered multiple regression analysis). P-value < 0.05 was considered significant.

Results

The basic clinical characteristics of the studied groups are shown in Table 1 and 2. Groups were matched for age, duration of hypertension, systolic blood pressure levels and the prevalence of the metabolic syndrome. We have not found in these groups any difference in the prevalence of glucose metabolism disorders and dyslipidemia at the time of our investigation. There were also no differences in the use of antidiabetic and hypolipidemic drugs among the studied groups.

As expected aldosterone levels were higher (91.7[58.0-104.4] vs. 243.0[163.3-327.0] ng/l) and potassium levels lower (4.2±0.4 vs. 3.7±0.4 mmol/l) in patients with PA, and between the two subtypes of PA, aldosterone levels were higher in patients with APA (243.0[170.9-333.7] vs. 195.0[160.5-258.4] ng/l). Basal cortisol levels were not statistically different between PA and EH patients but surprisingly we found significant differences in cortisol levels among patients with APA and IHA (448.1±94.2 vs. 615.4±114.5 nmol/l). Patients with IHA have significantly higher basal morning cortisol levels than patients with APA (all patients were studied at the same time in the morning), but there was no difference in the levels of 24h urinary cortisol (148.7[119.4-231.0] vs. 137.4[102.0-201.2] nmol/d) and in the cortisol levels after the short dexamethasone test (data not shown). In a subgroup analysis of patients with and without metabolic syndrome there was no difference in cortisol levels between the groups (data not shown).

The differences in inflammatory markers and PINP are summarized in Table 3 and 4. We found no differences in the levels of inflammatory markers (TNF-α, IL-6, hsCRP) among the studied groups, but there are significant differences in the levels of PINP between PA and EH group (35.18[28.46-41.16] vs. 45.21[36.95-62.81] ug/l). We have not found any gender related difference in the levels of PINP or inflammatory markers. There were no differences in the levels of Ca, P and ALP among the groups and none of the patients had a known metastatic process in bones, therapy of osteoporosis or recent fracture.

We found correlation between TNF-α levels and the prevalence of dyslipidemia, levels of HDL cholesterol and aldosterone levels, also correlation between monocytes and aldosterone and correlation between PINP and the use of statins, prevalence of hyperlipidemia and smoking but after multiple regression analysis none of them remained significant. There was no correlation between cortisol levels and inflammatory markers or PINP.

Discussion

Essential hypertension is associated with higher circulating levels of inflammatory cytokines (Peeters et al., 2001; Harrison et al., 2010). Dalekos et al. recently reported increased plasma concentrations of IL-1b in patients with EH, suggesting a possible involvement of this cytokine in EH (Dalekos et al., 1997). It is quite likely that other cytokines, such as TNF-α and IL-6 plays a role in the pathogenesis of hypertension by creating a cytokine milieu that promotes hypertension (Harrison et al., 2010). There is an accumulating body of evidence that alterations of the immune system are involved in the cascade of

events leading to hypertension. Increased circulating levels of immunoglobulins, various types of autoantibodies, decreased numbers and altered functions of T-lymphocytes, have been reported in patients with EH (Peeters et al., 2001). Also in knockout mice with lack of T and B lymphocytes is the hypertensive response to angiotensin-II infusion very altered (Guzik et al., 2007). What is interesting is mostly no elevation of T-cells are found in blood of hypertensives and the circulating concentrations of TNF, IL-1 and IL-6 did not differ between EH patients and controls (Peeters et al., 2001; Harrison et al., 2010). On the other hand, circulating levels of IL-1ra are elevated in hypertensive patients. An altered profile of pro- and anti-inflammatory cytokines in EH can be due to monocyte activation in the circulation (Peeters et al., 2001). It is possible that the cytokine abnormalities present in hypertension are reflecting only the monocyte activation induced by endothelial damage as a direct result of mechanical stress produced by hypertension (Harrison et al., 2010).

Very little is known about the profile of pro-inflammatory cytokines in the circulation of patients with primary aldosteronism. It seems that aldosterone has profibrotic effects based on an immunostimulatory state (Chatzikyriakou et al., 2008). In our study we have found no differences in circulating levels of cytokines between patients with EH and PA or APA and IHA. We cannot, however, exclude the differences in local cytokines synthesis between EH and PA as plasma levels might be too robust marker to evaluate subtle local concentrations. We do not expect any differences due to medication, all patients were on doxazosin and verapamil in order not to influence the renin-angiotensin- aldosterone system.

On the other hand we confirmed, that patients with PA have higher levels of PINP, marker of collagen synthesis (Stehr et al., 2010). As presented in a couple of studies (Peeters et al., 2001; Guzik et al., 2007; Harrison et al., 2010) in hypertensive subjects the perivascular fat is overwhelmed with activated immune cells, these activated immune cells are producing different types of cytokines. Cytokines can locally activate the collagen synthesis, which may cause fibrosis of the vessel wall. It is well established that changes in extracellular matrix proteins, namely collagen and elastin content, may play a relevant role in the development of cardiovascular damage in hypertension (Rizzoni et al., 2006). The results of Rizzoni (Rizzoni et al., 2006) indicating, that in small arteries of patients with primary aldosteronism, a pronounced fibrosis may be detected. Fibrosis is due to an increase in collagen and a decrease in elastin content within the tunica media (Intengan et al., 1999). The severity of fibrosis is greater than in blood-pressure-matched patients with EH but no significant correlation was observed between vascular collagen content and aldosterone levels (Rizzoni et al., 2006). Marked changes in the vessel wall, not only in small arteries, of patients with PA is confirmed also by increased aortic

stiffness in these patients measured by PWV (Strauch et al., 2006). The mechanism of aldosterone-induced fibrosis of the vessel wall is still unclear, aldosterone may increase collagen I synthesis and the number of endothelin receptors (Fullerton and Funder, 1994). Aldosterone has also a rapid nongenomic effect on the vessel wall mediated via activation of intracellular mineralocorticoid receptors (MR) (Funder, 2006). Through MR can aldosterone directly mediate effects in target organs independent of the regulatory roles of angiotensin II (Duprez, 2007) and MR receptors could be localized in endothelial and vascular smooth muscle cells (Bauersachs and Fraccarollo, 2006). Extra-adrenal synthesis of aldosterone in vascular wall and a localized paracrine effect may also play a role in vascular changes (Duprez, 2007). Aldosterone causes reduction in vascular fibrinolysis and has profibrotic effects based on an immunostimulatory state (Chatzikyriakou et al., 2008). The profibrotic actions of aldosterone, interestingly, seem to be independent of blood pressure, since mineralocorticoid receptor inhibition with eplerenon, a selective aldosterone blocker, decreases oxidative stress, inflammation, and fibrosis in mice with chronic pressure overload in the absence of a decrease in systemic blood pressure (Díez, 2007). Recent evidence shows that also angiotensin II is important in stimulating the production of reactive oxygen species and the activation of inflammatory mechanisms. Activation of the nuclear factor kappaB (NF-kappaB) stimulates the expression of genes important for expression of surface adhesion molecules and inflammation and stimulates the proliferation of lymphocytes and their activation (Luft, 2001). Angiotensin II also induces endothelin-1 expression in vascular adventitial fibroblasts, stimulating collagen accumulation (An et al., 2007).

We have not found any correlation between cortisol levels and PINP or the levels of inflammatory markers. The differences in cortisol levels between APA and IHA can be due to different basic/genotype of the two conditions. In almost 40% of patients with APA a mutation in KCNJ5 gene for K^+ channel was found (Boulkroun et al., 2012). These tumor-causing mutations alter the channel's selectivity filter. Mutant channels gain permeability to sodium, resulting in cellular depolarization and activation of voltage-gated calcium channels. The resulting calcium influx is sufficient to produce aldosterone secretion and cell proliferation, accounting for APA development (Scholl and Lifton, 2013). On the other hand in patients with idiopathic hyperaldosteronism the bilateral hyperplasia of the adrenal gland can affect not only cells of zona glomerulosa but also the cells of zona fasciculata which produce glucocorticoids. The difference in cortisol levels could explain partly our previous findings of different metabolic profiles of patients with APA and IHA. Patients with IHA have a higher prevalence of metabolic syndrome, higher prevalence of dyslipidemia with higher levels of triglycerides and lower levels of HDL cholesterol than patients with APA (Somlóová et al., 2012). The potential cortisol

overproduction in IHA compared to APA needs further investigation and it need to be confirmed in a large number of subjects.

Conclusion

In conclusion we have shown in our study that there are no differences in circulating levels of inflammatory markers such as TNF-α, IL-6 and hsCRP between patients with essential hypertension and patients with primary aldosteronism. It could be due to mostly local secretion of cytokines in the vessel wall. Because of the known profibrotic and proinflammatory effect of aldosterone we can presume that the measured circulating levels of inflammatory markers do not reflect the actual local levels of inflammatory markers in the arterial wall. The activation of inflammatory markers in the perivascular tissue in patients with primary aldosteronism can lead to vascular fibrosis. Our study has confirmed that patients with primary aldosteronism have higher levels of N-terminal propeptide of collagen I, marker of collagen synthesis, than patients with essential hypertension. The differences in the basal levels of cortisol between APA and IHA will need further investigation and confirmation on a bigger group of patients.

Limitations

The smaller number of patients in the subgroups of primary aldosteronism could have influenced the possible differences in plasma and serum concentration of inflammatory cytokines and also the differences in the basal cortisol levels. A possible influence of higher bone turnover on PINP levels could not be excluded because none of our patient had parathormone and D vitamin levels measured.

Acknowledgements

This work was supported by Charles University research project PRVOUK No. P35/LF1/5

Conflict of interest

The authors declare no conflict of interest.

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Table 1- Basic characteristics- essential hypertension vs. primary aldosteronism										
		EH					PA			p
Variable	n					n				
Sex (men %)	15	52%				15	54%			NS
Age, y	28	46,8	±	12,4		28	49,3	±	8,1	NS
Duration of hypertension, y	28	9,0	±	8,7		28	8,7	±	7,4	NS
BMI, kg/m2	28	30,2	±	5,4		28	29,9	±	3,1	NS
Systolic BP in 24h, mmHg	28	141,4	±	11,5		27	146,8	±	14,8	NS
Diastolic BP in 24h, mmHg	28	83,6	±	6,9		27	88,9	±	9,7	0,02
HR in 24h, min-1	28	70,8	±	7,2		27	67,5	±	7,3	NS
Serum sodium, mmol/l	28	140,9	±	2,1		28	143,3	±	2,5	<0.001
Serum potassium, mmol/l	28	4,2	±	0,4		28	3,7	±	0,4	<0.001
Serum creatinin, umol/l	28	72,1	±	18,1		28	70,6	±	14,2	NS
Glucose level, mmol/l	28	5,5	±	1,5		28	5,2	±	0,7	NS
Total cholesterol, mmol/l	28	5,1	±	1,2		28	5,1	±	1,2	NS
Triglycerides, mmol/l	28	1,6	±	0,8		28	1,3	±	0,8	NS
HDL cholesterol, mmol/l	28	1,4	±	0,4		27	1,3	±	0,3	NS
LDL cholesterol, mmol/l	28	3,0	±	1,1		27	3,1	±	1,0	NS
Plasma aldosteron, ng/l	28	91,7	(58-104,4)			28	243,0	(163.3-327.0)		<0.001
PRA, ug/l/h	25	0,6	(0.4-1.1)			24	0,4	(0.3-0.5)		<0.001
DRC, pg/ml	3	3,8	(1.7-10.7)			4	2,5	(1.7-3.3)		NS
ARR, ng/dl//ng/ml/h	25	11,4	(5.8-22.2)			24	66,9	(42.9-101.6)		<0.001
ARR, ng/dl//ng/l	2	2,3	(1.3-3.4)			4	28,0	(8.4-55.7)		NS
Basal cortisol levels, nmol/l	28	566,2	±	149,7		24	486,3	±	139,5	NS
24h urinary cortisol levels, nmol/d	27	150,4	(98-200.5)			26	149,9	(119.4-226.0)		NS
Abbreviation: EH-essential hypertension, PA- primary aldosteronism, BMI- body mass index, BP- blood pressure,										
HR- heart rate, PRA- plasma renin activity, DRC- direct renin concentration, ARR- aldosteone to renin ratio										
Data are expressed as means ± SD or median (interquartile range, 25th-75th percentile). P-value < 0.05 was considered significant.										

Table 2- Basic characteristics- aldosterone producing adenoma vs. idiopathic hyperaldosteronism									
		APA				IHA			p
Variable	n				n				
Sex (men %)	6	50%			6	60%			NS
Age, y	12	48,8	±	7,7	10	49,4	±	8,3	NS
Duration of hypertension, y	12	9,1	±	7,2	10	7,9	±	6,1	NS
BMI, kg/m2	12	30,2	±	3,8	10	28,9	±	2,5	NS
Systolic BP in 24h, mmHg	12	146,8	±	16,3	9	145,0	±	16,6	NS
Diastolic BP in 24h, mmHg	12	89,1	±	11,5	9	86,6	±	9,4	NS
HR in 24h, min-1	12	66,3	±	8,3	9	68,4	±	8,3	NS
Serum sodium, mmol/l	12	143,6	±	2,8	10	143,3	±	2,3	NS
Serum potassium, mmol/l	12	3,5	±	0,4	10	3,9	±	0,4	NS
Serum creatinin, umol/l	12	67,3	±	14,7	10	72,8	±	12,4	NS
Glucose level, mmol/l	12	5,2	±	0,5	10	5,0	±	0,5	NS
Total cholesterol, mmol/l	12	5,1	±	1,2	10	5,2	±	1,3	NS
Triglycerides, mmol/l	12	1,2	±	0,9	10	1,3	±	0,6	NS
HDL cholesterol, mmol/l	12	1,4	±	0,4	10	1,3	±	0,2	NS
LDL cholesterol, mmol/l	12	3,2	±	1,0	10	3,4	±	1,1	NS
Plasma aldosteron, ng/l	12	243,0	(170.9-333.7)		10	195,0	(160.5-258.4)		NS
PRA, ug/l/h	10	0,3	(0.2-0.4)		9	0,4	(0.3-0.5)		NS
DRC, pg/ml	2	3,3	(2.5-4.1)		1	2,4	±	0,0	NS
ARR, ng/dl//ng/ml/h	10	101,4	(49.9-169.6)		9	50,2	(39.9-59.7)		NS
ARR, ng/dl//ng/l	2	27,8	(7.8-47.8)		1	9,1	±	0,0	NS
Basal cortisol levels, nmol/l	11	448,1	±	94,2	8	615,4	±	114,5	0,002
24h urinary cortisol levels, nmol/d	11	148,7	(119.4-231.0)		9	137,4	(102.0-201.2)		NS
Abbreviation: APA- aldosterone producing adenoma, IHA- idiopathic hyperaldosteronism, BMI- body mass index, BP- blood pressure,									
HR- heart rate, PRA- plasma renin activity, DRC- direct renin concentration, ARR- aldosteone to renin ratio									
Data are expressed as means ± SD or median (interquartile range, 25th-75th percentile). P-value < 0.05 was considered significant.									

Table 3- Inflammatory markers- essential hypertension vs. primary aldosteronism									
		EH				PA			p
Variable	n				n				
Leukocytes, 10^9/l	28	6,35	±	1,42	28	5,97	±	1,29	NS
Neutrophils, 10^9/l	28	3,56	±	1,2	28	3,53	±	1,02	NS
Lymphocytes, 10^9/l	28	1,99	±	0,55	28	1,77	±	0,46	NS
Monocytes, 10^9/l	28	0,54	±	0,16	28	0,45	±	0,14	NS
hsCRP, mg/l	28	0,53	(0.25-1.54)		28	0,37	(0.31-0.61)		NS
IL-6, pg/ml	27	0,94	(0.70-1.13)		28	0,97	(0.71-1.28)		NS
TNF-α, pg/ml	28	5,09	(3.68-6.32)		27	4,84	(3.62-6.50)		NS
PINP, ug/l	28	35,18	(28.46-41.16)		28	45,21	(36.95-62.81)		0,003
Abbreviation: EH-essential hypertension, PA- primary aldosteronism, hsCRP- high senstivity C-reactive protein, IL-6- interleukin 6,									
TNF-α- tumor necrosis factor alpha, PINP- N-terminal propetid of collagen I.									
Data are expressed as means ± SD or median (interquartile range, 25th-75th percentile). P-value < 0.05 was considered significant.									

Table 4- Inflammatory markers- aldosterone producing adenoma vs. idiopathic hyperaldosteronism									
		APA				IHA			p
Variable	n				n				
Leukocytes, 10^9/l	12	6,37	±	1,41	10	5,71	±	1,21	NS
Neutrophils, 10^9/l	12	3,78	±	0,98	10	3,31	±	1,2	NS
Lymphocytes, 10^9/l	12	1,83	±	0,51	10	1,79	±	0,47	NS
Monocytes, 10^9/l	12	0,47	±	0,14	10	0,48	±	0,14	NS
hsCRP, mg/l	12	0,34	(0.29-0.47)		10	0,75	(0.36-1.11)		NS
IL-6, pg/ml	12	0,96	(0.63-1.21)		10	0,90	(0.65-1.06)		NS
TNF-α, pg/ml	12	4,54	(3.62-7.03)		9	5,19	(4.23-5.27)		NS
PINP, ug/l	12	46,48	(28.89-63.55)		10	52,12	(41.03-63.57)		NS
Abbreviation: APA-aldosterone producing adenoma, IHA- idiopathic hyperaldosteronism, hsCRP- high senstivity C-reactive protein,									
IL-6- interleukin 6, TNF-α- tumor necrosis factor alpha, PINP- N-terminal propetid of collagen I.									
Data are expressed as means ± SD or median (interquartile range, 25th-75th percentile). P-value < 0.05 was considered significant.									