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Influence of ATII Blockers and Calcium Channel Blockers on Renal Vascular Resistance in Patients with Essential Hypertension

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A B S T R A C T

Doppler can evaluate renal vascular resistance, and resistance index (RI) highly correlates with blood pressure and renal function in various pathological conditions. Purpose of the study was to measure and compare renal Doppler indices in patients with newly-diagnosed essential hypertension (EH) and in healthy subjects; to determine changes of Doppler indices in patients after six-months monotherapy with either the AT II blocker (valsartane) or calcium channel blocker (niphedipine); to determine which drug has better renoprotective effect. 65 healthy controls were examined, as well as 69 patients with the newly-diagnosed EH, without signs of the target organ damage. Duplex Doppler US of interlobar intrarenal arteries was performed, and RI, acceleration index (AI) and acceleration time (AT) measured. Antihypertensive monotherapy was performed with vaslartane in 34 patients and with niphedipine in 35 patients. Doppler was repeated after the six-months therapy. RI in patients with the 1. stage of EH is significantly higher compared to the controls ($p<0.001$), and significantly lower compared to the stage 2. of EH ($p<0.001$). The significant decrease of systolic ($p<0.001$) and dyastolic blood pressure (BP) ($p<0.001$) was noted after the therapy. RI in healthy examinees ($RI=0.59\pm0.023$) is significantly lower than in EH ($RI=0.66\pm0.26$) ($p<0.001$), while AI is significantly higher ($p<0.001$), and AT is significantly lower ($p<0.001$). In patients treated with valsartane and those treated with niphedipine, the RIs are significantly lower than before ($p<0.001$), while AIs were significantly higher, and ATs were significantly lower after the therapy after the therapy with both drugs. RIs in patients treated with valsartane ($RI = 0.615 \pm 0.036$) are significantly lower than RIs of patients treated with niphedipine ($RI=0.642\pm0.030$) ($p<0.01$) after therapy. Regression analysis for the predictive values of RI, AT, AI in relation to the age-standardized values of systolic and diastolic BP of healthy examinees and patients with hypertension has demonstrated that RI is the strongest and statistically significant predictor in all groups of examinees. Six-months monotherapy of EH with valsartane or with niphedipine is equally efficient in the decrease of the blood pressure, but valsartane has more favourable effect on kidney. Resistance index measured in intrarenal arteries is the best parameter of Doppler spectrum in the evaluation of the effects of antihypertensive therapy on the kidney.

Key words: *Doppler, ultrasound, renal vascular resistance, essential hypertension, antihypertensive treatment*

Introduction

Hypertension is the major risk-factor for the development of cardiovascular diseases, and the most important goal of the antihypertensive treatment is to prevent the cardiovascular morbidity and mortality. Large clinical studies have conclusively demonstrated that lowering of the blood pressure reduces the risk of major cardiovascular events[1,2], although only approximately one third of hypertensive patients obtain adequate medical regulation of blood pressure[3]. Additional risk factors, like elevated blood cholesterol level, diabetes, smoking, and renal disease affect the outcome of hypertension[4]. Even the

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mild renal insufficiency is associated with the additional cardiovascular events in hypertensive patients[5]. The most important system for the regulation of blood pressure and water and sodium metabolism is the renin-angiotensine system. Renin is the enzyme secreted by the kidney iuxtaglomerular system and is associated with the secreation of aldosterone and production of the angiotensin II[6]. Antihypertensive medications are very numerous, and their effects on kidneys are studied in numerous publications. Patients with uncomplicated hypertension are usually treated with monotherapy, while patients with complicated hypertension need therapy with two or more medications to achive sattisfactory blood pressure control[2,6–9]. The most common hypertensive lesions of renal blood vessels are atherosclerotic lesions of afferent and efferent arteriolae and glomerular capillaries, that result in the decrease of glomerular filtration and tubular dysfunction[10,11]. One of the hystopathologic changes observed is myointimal hyperplasisa of interlobular arteries, with the reduction of arterial lumen. Also focal or global segmental sclerosis is observed. Nephroangiosclerosis results in elevated renal vascular resistance[12,13]. Color duplex Doppler ultrasound can demonstrate blood flow in intrarenal arteries and enables estimation of renal vascular resistance by measuring renal resistance index (RI) after spectral waveform analysis is performed[14,15].

The aims of the study are following: (1) to measure the Doppler resistance index (RI), acceleration time (AT) and acceleration index (AI) in interlobar intrarenal arteries of patients with the newly diagnosed essential hypertenison and in the control group of healthy subjects and evalute differences between these groups; (2) to determine changes of RI, AT, AI of hypertensive patients after six-months monotherapy with AT II blocker (valsartane) or with calcium-channel blocker (niphedipine); (3) to determine which of the two antihypertensive medications has better effect on analyzed Doppler parameters, i.e. better therapeutic effect on the kidney.

Materials and Methods

Sixty-nine patients with newly diagnosed essential hypertension (30 women, 39 men, average age 49.6 years, range 35–60 years) were included into the study. They were examined in the period of 44 months. The diagnosis of essential hypertension was established after the meticulous hisotry, physical exam, complete laboratory analysis of blood and urine. The presence and the degree of the damage of target organs were evaluated by ECG, ocular fundus exam and urinalysis; patients with the evidence of the target organ damage were excluded from the study. In all patients B-mode and color-duplex Doppler US exam of kidneys and renal arteries was performed. Additional tests were performed to exclude secondary hypertension when necessary. All patients with ultrasound findings suggesting secondary hypertension (evidence for renal artery stenosis, asymmetry in renal size – difference of renal length >2 cm, hyperechoic renal parenchyma, masses in adrenal glands, hydronephrosis, etc.) were excluded from the study. Hypertension was defined according to the JNC VII (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure) criteria as average blood pressure ≥140/90 mmHg in at least three measures in various situations, and patients were included into the study with the first and second degree of hypertension according to the JNC VII criteria[2], which is equivalent to the mild and moderate hypertension according to the ESH/ESC (European Society of Hypertension and European Society of Cardiology) classification[16,17]. Informed consent was obtained by all examinees, and Institutional Ethical Board consented with the study. Patients were excluded from the study with tumors, liver diseases, chronic cardiac failure, diabetes mellitus, renal insufficiency, obese people (body mass index >30), patients with psychological diseases, dementia, and other diseases that render examinees uncooperable. Patients were on the normal diet, with no salt restriction, and were not treated by antihypertensive medications previously.

The control group of healthy examinees, mostly volunteers, consists of 65 healthy subjects (25 women and 40 men, average age 47.1 years, range 36–60 years), who are normotensive, without acute or chronic diseases in history that could affect renal circulation (absence of renal, pulmonary and systemic diseases and diabetes mellitus), with normal urinalysis, and normal morphologic B-mode ultrasound findings of kidneys. All healthy examinees gave informed consent to the study.

Arterial blood pressure (BP) was measured in sitting position after five minutes of rest. Systolic and diastolic blood pressure were determined with the precision of 2 mm Hg, and they were measured three times in a row, in a period of five minutes, and average values of three measurements were taken for the value of systolic and diastolic blood pressure. Hypertension was considered when BP values were ≥140/90 mmHg. In all patients BP was measured on the day when the study commenced, and after six-months of antihypertensive monotherapy. Patients were routinelly controlled twice a month to modify the dose of the medication. Following laboratory tests of blood and urine were performed: creatinine, urea, potassium, sodium, choloride, uric acid, cholesterol, LDL cholesterol, HDL cholesterol, glucose, ALT, AST, LDH, CPK, billirubin, complete red and white blood count, complete urinalysis, creatinine clearance, 24-hours protein excretion in urine. All laboratory analysis were performed using the standard, established methods in general usage. Body mass index was calculated according to the formula: body weight (kg)/height^2, a patients with the BMI >30 were considered to be obese.

Antihypertensive monotherapy was performed with ATII blocker valsartane 80–160 mg (Diovan®, produced by Novartis) in a group of 34 patients, and with calcium-chanel blocker niphedipine up to 40 mg/daily (Cordipin retard®, produced by Krka) in 35 patients. Dosage modification was dependant on BP values measured at the control examinations.

Ultrasound exams were performed using state-of-the--art ultrasound scanners Logiq 9 (General Electric Healthcare, Milwaukee, WI, USA) and HDI 5000 (Advanced Technology Laboratories, Bothel, WA, USA), equiped with multifrequency/broad-bandwith convex electronic transducers in the frequency ragne of 2.5–5 MHz, with the advanced software capabilities (native harmonic, automatic image optimization, multiple focal zones, compound imaging, etc). First the B-mode US exam of kidneys was performed, and lenght and parenchymal thickness were recorded and evaluated. Only patients with simple renal cysts with diameter <5 cm were not excluded, while all other patients with renal abnormalities were excluded from the study (small kidney, pelvicaliectasis, renal stones, nephrocalcinosis, masses, ADPKD, etc). After that color duplex Doppler exam was performed in the left or right decubitus postion of the patient. Spectral waveform analysis was performed in interlobar arteries, at three typical sites (upper, middle and lower pole of the kidney). Resistance index (RI) was measured, as well as acceleration time (AT) and acceleration index (AI). Mean value from all three measurements was calculated for the each Doppler parameter. All patients with »parvus-tardus« spectra, indicating renal artery stenosis, were excluded from the study. RI is the difference of maximum systolic velocity and minimum diastolic velocity, divided by maximum systolic velocity. AT is the time from the beginning of the cycle to the early systolic peak. AI reflects the steepness of the acceleration phase of spectral curve, and is calculated as $\Delta v/\Delta t$ and expressed in m/s^2. The lowest pulse repetition frequency that does not cause alliasing was used in all measurements. Wall filter <25 Hz was used, as well as maximal priority lever for color. Angle correction was applied in all measurements, with the angle between US beam and the vessel below 60°. Spectra in main renal arteries were also analyzed and peak systolic velocities measured. They were <1.5 m/s in all patients. The duration of exams was 30–45 minutes. Only those examinees were included where optimal intrarenal arterial Doppler spectra could be demonstrated and all analyzed parameters measured. Power Doppler was not used since the quality of color Doppler was excellent and enabled equisite demonstration of intrarenal flow and of spectral analysis.

The measured values of RI, AT, AI and blood pressure are expressed as mean values±SD, and median values. RI, AT and AI values were compared between healthy controls and group of hypertensive patients before the commencement of medical treatment. After that, values of Doppler parameters were compared in each individual patient at the beginning of treatment, and after six--months antihypertensive monotherapy. The changes were analyzed separately in the group of patients taking AT II blocker and in the group of patients taking calcium-channel blocker, and differences between these two groups were compared.

The distribution of all quantitative variables was tested in the group and in time for normal distribution using Smirnov-Kolmogornov test. When distribution was normal parametric tests were used in the analysis (Student's t-test and t-test for paired samples), while when distribution was not normal non-parametric tests were used (Mann-Whitney test, Wilcoxonov paired-rank test). The differences in distributions of qualitative variables were tested with χ^2-test. Predictive value of RI, AT and AI in relation to the blood pressure as criterium variable was evaluated by using regression analysis.

Results

Among quantitative variables only distributions of acceleration time (AT) in various combinations (in the group, before and after the therapy) have demonstrated distribution which is not normal. All other variables had normal distribution.

Correlation of RI values and systolic and diastolic blood pressures were analyzed. In all 134 examinees (healthy examinees and hypertensive patients before therapy) statistically significant correlation (Pearson's test) was observed between RI and systolic blood pressure ($p<0.001$, CC 0.93), and between RI and diastolic blood pressure ($p<0.001$, CC 0.89). RI has also statistically significant correlation with the age ($p<0.001$, CC 0.54).

The average age of healthy examinees in the control group was 47.1±7,3 (range 35–60) years, and average age of hypertensive patients was 49.6±7,1 (range 35–60) years. Paired T-test has not demonstrated statistically significant difference ($p=0.06$).

The descriptive data for healthy examinees in the control group (N=65) is shown in Table 1.

TABLE 1
DESCRIPTIVE DATA FOR HEALTHY EXAMINEES IN THE CONTROL GROUP (N=65)

	RI	AT (ms)	AI (m/s^2)	Sist (mmHg)	Diast (mmHg)	Age (years)
$\overline{X}$	0.59	21.69	8.06	125.6	73.6	47.1
Median	0.59	20	8	130	72	46
SD	0.023	16.6	0.78	8.93	6.42	7.34
Min	0.55	10	6	105	60	35
Max	0.65	15	9.7	138	86	60

RI – resistance index, AT – acceleration time, AI – acceleration index, Sist – systolic blood pressure, Diast – diastolic blood pressure, Age, min – minimum, max – maximum

The descriptive data for all hypertensive patients (N=69) before (0) and after the therapy (1) are presented in Table 2.

T-test has demonstrated the significant decrease of systolic blood pressure ($p<0.001$) and diastolic blood pressure ($p<0.001$) after therapy in relation to the values before the therapy.

T-test has demonstrated statistically significant differences in values of RI and AI, and Mann-Whitney test demonstated statistically significant differences in values of AT between healthy examinees in the control group and the group of all patients with essential hypertension. RI in heatlhy examinees (RI=0.59±0.023) is significantly lower compared to hypertensive patients (RI=0.66±0.26) ($p<0.001$), and AI in healthy examinees (AI=8.06±0.78 m/s^2) is significantly higher than in the hypertensive patients (AI=5.27±1.47 m/s^2) ($p<0.001$). Acceleration time is significantly lower in healthy examinees (21.7±16.6 ms) compared to hypertensive patients (38.6±8 ms) ($p<0.001$).

The average age of hypertensive patients treated with valsartane was 49.7±6.8 years, while average age of hypertensive patients treated with niphedipine was 49.5±7,5 years. Paired T-test has not shown statistically significant difference ($p=0.9$).

The descriptive data for hypertensive patients treated with niphedipine (N=35) before (0) and after therapy (1) are demonstrated in Table 3.

TABLE 2
DESCRIPTIVE DATA FOR 69 HYPERTENSIVE PATIENTS BEFORE (0) AND AFTER THE THERAPY (1)

	RI-0	RI-1	AT-0 (ms)	AT-1 (ms)	AI-0 (m/s^2)	AI-1 (m/s^2)	Sist-0 (mmHg)	Sist-1 (mmHg)	Diast-0 (mmHg)	Diast-1 (mmHg)
$\overline{X}$	0.659	0.629	38.62	34.57	5.27	6.09	157.9	135.0	99.7	81.3
Median	0.66	0.62	40	30	5	6.0	155	135	100	80
SD	0.026	0.035	8.04	7.94	1.47	1.53	10.15	8.05	5.25	5.87
widctlparMin	0.61	0.56	20	20	3	3.0	142	120	88	70
Max	0.71	0.72	55	50	8.8	8.8	178	160	109	100

RI – resistance index, AT – acceleration time, AI – acceleration index, sist – systolic blood pressure, Diast – diastolic blood pressure, min – minimum, max – maximum

TABLE 3
DESCRIPTIVE DATA FOR 35 HYPERTENSIVE PATIENTS TREATED WITH NIPHEDIPINE BEFORE (0) AND AFTER THE THERAPY (1)

	RI-0	RI-1	AT-0 (ms)	AT-1 (ms)	AI-0 (m/s^2)	AI-1 (m/s^2)	Sist-0 (mmHg)	Sist-1 (mmHg)	Diast-0 (mmHg)	Diast-1 (mmHg)
$\overline{X}$	0.657	0.642	38.29	35.86	5.27	5.69	158.6	136.4	99.8	81.9
Median	0.65	0.63	40	35	5	5.2	155	135	100	82
SD	0.026	0.03	7.66	7.90	1.58	1.55	9.56	6.83	5.04	5.74
Min	0.61	0.59	20	20	3	3.4	145	120	88	70
Max	0.71	0.70	55	50	8.8	8.4	175	160	108	100

RI – resistance index, AT – acceleration time, AI – acceleration index, sist – systolic blood pressure, Diast – diastolic blood pressure, min – minimum, max – maximum

TABLE 4
DESCRIPTIVE DATA FOR 34 HYPERTENSIVE PATIENTS TREATED WITH VALSARTANE BEFORE (0) AND AFTER THE THERAPY (1)

	RI-0	RI-1	AT-0 (ms)	AT-1 (ms)	AI-0 (m/s^2)	AI-1 (m/s^2)	Sist-0 (mmHg)	Sist-1 (mmHg)	Diast-0 (mmHg)	Diast-1 (mmHg)
$\overline{X}$	0.661	0.613	38.97	33.24	5.27	6.5	157.3	133.6	99.6	80.7
Median	0.66	0.61	40	30	5.1	6.85	153	135	100	80
SD	0.026	0.036	8.51	7.87	1.36	1.42	10.82	9.02	5.53	6.03
Min	0.61	0.56	20	20	3.2	3.0	142	120	88	70
Max	0.71	0.72	55	50	8.4	8.8	178	160	109	95

RI – resistance index, AT – acceleration time, AI – acceleration index, sist – systolic blood pressure, Diast – diastolic blood pressure, min – minimum, max – maximum

The descriptive data for hypertensive patients treated with valsartane (N=34) before (0) and after therapy (1) are demonstrated in Table 4.

T-test has not shown statistically significant differences in RI values before the treatment between groups of hypertensive patients later treated with niphedipine and with vaslartane (p=0.62). Likewise, t-test has not shown significant diffrences in values of AI between these two groups of patients (p=0.99). Mann-Whitney test has not shown significant differences in values of AI between these two groups of patients (p=0.71).

In patients treated with valsartane, RI was significantly lower after therapy compared to values before the therapy (t-test, $p<0.001$). Likewise, in patients treated with niphedipine RI was significantly lower after therapy ($p<0.001$). AI values were significantly higher after therapy both in the valsartane group (t-test, $p<0.001$) and niphedipine (t-test, $p<0.001$). AT values were significantly lower (Wilcoxon signed ranks test) after therapy both in patients treated with valsartane ($p<0.001$) and those treated with niphedipine ($p<0.003$).

The differences in values of RI between patients treated with valsartane and those treated with niphedipine were significantly different after six months of therapy. In patients treated with valsartane mean RI was 0.615±0.036, siginificantly lower than in patients treated with niphedipine, where mean RI was 0.642±0.030) ($p<0.01$, t-test). Likewise, AI in patients treated with vaslartane (AI=6.5±1.42) was significantly higher than in patients treated with niphedipine (AI=5.7±1.55) ($p<0.03$, t-test).

Mann-Whitney test has not shown significant differences in values of AT after treatement between patients treated with valsartane and niphedipine (p=0.19).

All measured varibles (systolic, diastolic and mean BP, pulse pressure, RI, AT, AI) have positive correlation with age ($p<0.01$ for all variables), and all of these values are age-adjusted. All variables have normal distribution within the group, which enables regression analysis. Regression analysis was performed for the predictive values RI, AT, AI in relation to the age-standardized values of systolic and diastolic BP of healthy examinees and hypertensive patients.

The results of regression analysis are demonstrated in the following Tables 5–8.

It is visible that for age-standardized systolic BP the significant predictor is age-adjusted resistance index, both in hypertensive patients and in healthy subjects,

TABLE 5
REGRESSION ANALYSIS FOR THE DEPENDANT VARIABLE OF AGE-STANDARDIZED SYSTOLIC BLOOD PRESSURE IN RELATION TO PREDICTORS OF AGE-STANDARDIZED RESISTANCE INDEX, ACCELERATION TIME AND ACCELERATION INDEX FOR HYPERTENSIVE PATIENTS

				Nonstand	k	Stand. k	t	p
	$\overline{X}$	SD	N	B	SE	Beta		
(Constant)				–79.44	21.39		–3.714	0.0001
a-s-SBP	143.46	8.31	69					
a-s-RI	0.629	0.023	69	364.6	31.43	0.997	11.60	0.0001
a-s-AT	0.031	0.004	69	–105.4	118.17	–0.048	–0.892	0.376
a-s-AI	6.49	0.90	69	–0.476	0.626	–0.052	–0.759	0.45

a-s-SBP – age-standardized systolic blood pressure, a-s-RI – age-standardized resistance index, a-s-AT – age-standardized acceleration time, a-s-AI – age-standardized acceleration index, SE – standard error, k – coefficient

TABLE 6
REGRESSION ANALYSIS FOR THE DEPENDANT VARIABLE OF AGE-STANDARDIZED SYSTOLIC BLOOD PRESSURE IN RELATION TO PREDICTORS OF AGE-STANDARDIZED RESISTANCE INDEX, ACCELERATION TIME AND ACCELERATION INDEX FOR HEALTHY SUBJECTS

				Nonstand	k	Stand. k	t	p
	$\overline{X}$	SD	N	B	SE	Beta		
(Constant)				38.44	34.63		1.11	0.271
a-s-SBP	140.98	8.60	65					
a-s-RI	0.622	0.024	65	207.8	44.04	0.568	4.72	0.0001
a-s-AT	0.030	0.004	65	2.594	60.98	–0.001	0.043	0.966
a-s-AI	6.77	0.94	65	–3.946	1.11	–0.431	–3.572	0.001

a-s-SBP – age-standardized systolic blood pressure, a-s-RI – age-standardized resistance index, a-s-AT – age-standardized acceleration time, a-s-AI – age-standardized acceleration index, SE – standard error, k – coefficient

TABLE 7
REGRESSION ANALYSIS FOR THE DEPENDANT VARIABLE OF AGE-STANDARDIZED DIASTOLIC BLOOD PRESSURE IN RELATION TO PREDICTORS OF AGE-STANDARDIZED RESISTANCE INDEX, ACCELERATION TIME AND ACCELERATION INDEX FOR HYPERTENSIVE PATIENTS

				Nonstand	k	Stand. k	t	p
	$\overline{X}$	SD	N	B	SE	Beta		
(Constant)				–56.24	19.61		–2.87	0.006
a-s-DBP	87.73	5.16	69					
a-s-RI	0.629	0.023	69	217.32	28.82	0.957	7.54	0.0001
a-s-AT	0.031	0.004	69	152.91	108.3	0.113	1.41	0.966
a-s-AI	6.49	0.90	69	0.4	0.574	0.07	0.694	0.001

a-s-DBP – age-standardized diastolic blood pressure, a-s-RI – age-standardized resistance index, a-s-AT – age-standardized acceleration time, a-s-AI – age-standardized acceleration index, SE – standard error, k – coefficient

TABLE 8
REGRESSION ANALYSIS FOR THE DEPENDANT VARIABLE OF AGE-STANDARDIZED DIASTOLIC BLOOD PRESSURE IN RELATION TO PREDICTORS OF AGE-STANDARDIZED RESISTANCE INDEX, ACCELERATION TIME AND ACCELERATION INDEX FOR HEALTHY SUBJECTS

				Nonstand	k	Stand. k	t	p
	$\overline{X}$	SD	N	B	SE	Beta		
(Constant)				5.76	21.75		0.265	0.792
a-s-DBP	86.27	5.30	65					
a-s-RI	0.622	0.024	65	149.5	27.66	0.663	5.4	0.0001
a-s-AT	0.030	0.004	65	8.21	38.29	–0.006	0.214	0.831
a-s-AI	6.77	0.94	65	–1.87	0.69	–0.331	–2.69	0.009

a-s-DBP – age-standardized diastolic blood pressure, a-s-RI – age-standardized resistance index, a-s-AT – age-standardized acceleration time, a-s-AI – age-standardized acceleration index, SE – standard error, k-coefficient

while age-adjusted AT and AI are not significant predictors in hypertensive patients. AI is significant predictor in healthy examinees. Standardized coefficient β is higher for RI than for AI (0.57 *vs*. –0.43). For age-standardized diastolic BP the significant predictor is age-adjusted resistance index in hypertensive patients, while RI is significant predictor also in healthy subjects. AI is also significant predictor in healthy examinees, while other predictors are not statistically significant. Standardized coefficient β is twice higher for RI than for AI (0.66 *vs*. –0.33).

It was analyzed whether RI in hypertensive patients with the first stage of EH (140–159/90–99 mm Hg) is significantly lower compared to the patients in the second stage of hypertension (160–179/100–109 mm Hg), and significance of differences was tested using the t-test.

The descriptive values of RI in hypertensive patients in the first stage and in the second stage of hypertension, as well as in healthy examinees, are shown in the Table 9.

T-test has shown that RI values in hypertensive patients with the first stage of hypertension are statistically significnatly higher compared to the group of healthy controls ($p<0.001$), while they are significantly lower as compared to patients with the second stage of hypertension ($p<0.001$).

Discussion

In essential hypertension kidneys are inevitably affected with arteriolar pathologic changes, and renal blood flow may be reduced as a result of arteriolar constriction, even in the early phase of essential hypertension. Older patients with essential hypertension have high total peripheral resistance as a result of atherosclerosis of intra-

TABLE 9
THE DESCRIPTIVE VALUES OF RESISTANCE INDICES IN HYPERTENSIVE PATIENTS IN THE FIRST STAGE AND IN THE SECOND STAGE OF HYPERTENSION AND IN HEALTHY EXAMINEES

	RI-0	RI-1	RI-2
$\overline{X}$	0.590	0.638	0.670
SD	0.023	0.013	0.025
SE	0.003	0.003	0.004
N	65	23	46

RI-0 – resistance index in healthy examinees, RI-1 – resistance index of patients in the first stage of hypertension, RI-2 – resistance index of patients in the second stage of hypertension, SE – standard error, N – number of examinees/patients

renal arteries. Elevated Doppler resistance index in mild hypertension or in the early phase of essential hypertension is most probably associated with the functional vasoconstriction, while in the moderate hypertension and long-standing hypertension elevated RI may be result of hypertensive nephrosclerosis[16–18]. Renal vascular resistance is regulated by the balance of several vasodilatory and vasoconstrictory systems, and any disbalance in these systems leads to renal vasoconstriction and causes hypertension[12].

Doppler is established noninvasive investigation for evaluation of flow in renal arteries and veins, and intrarenal arteries. Duplex Doppler ultrasound has been used in last fifteen years in numerous studies of renal vascular resistance in various pathologic renal conditions, and it was shown that renal resistance index (RI) correlates highly with blood pressure and renal function[18–21]. Renal RI is indicator of renal vascular resistance, and its elevation reflects well intrarenal vasoconstriction. Elevated RI is thus observed in conditions like acute renal failure, acute tubular necrosis, acute and chronic renal transplant rejection, diabetic nephropathy, lupus nephropathy, hemolitic-uremic syndrom, autosomal policystic kidney disease, obstructive nephropathy, chronic glomerular and interstitial renal diseases, etc[18–23]. Elevated RI is thus associated with intrarenal arteriolar and glomerular sclerosis, and presence and degree of interstitial impairment in renal parenchymal diseases. RI is considered to be elevated if values are ≥0.70. RI is also measured in diagnosis of renal artery stenosis (RAS) and renovascular hypertension, since it is well know that high degree RAS affects morphology of intrarenal arterial spectra, resulting in parvus-tardus spectra with decreased RI, prolonged acceleration time and decreased acceleration index[24].

The role of duplex Doppler ultrasound in evaluation of renal vascular resistance in essential hypertension is still not well determined, and relatively few papers were published, that demonstrated elevated RI with the progression of hypertension, and good correlation of RI values with functional renal tests, stage and duration of hypertension, and patient's age. Since elevation of RI is associated with macrovascular atherosclerotic changes in hypertensive patients that also have diabetes, as well as with increased blood pressure and duration of the disease in patients with essential hypertension, it is considered that RI may reflect intraparenchymal impairment and may serve as indicator of hypertensive renal impairment[18–20].

There are only few studies about effects of treatment with differenct antihypertensive drugs on renal vascular resistance in patients with essential hypertension[25]. Elevated RI is partially consequence of functional vascular changes – vasoconstriction that is result of activation of sympatic system and circulating noradrenalin or angiotensine II, endoteline, prostacycline, and nitric-oxyde. Therefore, in some cases elevation of RI may be reversible, and potential reversibility was studied during the treatment with lisinoprile; in many studies it was shown that ACE inhibitors may protect, and even enhance glomerular filtration rate in hypertensive patients. Protective effect of lisinoprile on renal function may be explained by the ability of ACE inhibitors to reduce renal vascular resistance[18,26,27]. It seems that the choice of antihypertensive drug affects the outcome of renal impairment in essental hypertension and that the addition of ACE inhibitors to other drugs results in much better outcome of renal disease in patients with nephrosclerosis[28]. AT II blockers, like valsartane, have many favourable effects in addition to lowering of blood pressure; they do not change glomerular filtration, while they enhance natriuresis. It is assumed that AT II blockers will ameliorate cardiovascular and renal prognosis of patients with chronic renal failure[29,30].

When renal Doppler was used to evaluate treatment of hypertension, most commonly resistance index (RI) was measured, and in few studies PI and peak systolic velocities. Other potentially important parameters of Doppler spectrum, like acceleration time (AT), acceleration index (AI), and early systolic peak (ESP) were not studied. AT, AI and ESP are very important in the assessment of patients with hemodinamically significant renal artery stenosis and renovascular hypertension. They are affected also by the vessel compliance, and one might assume that they may complement Doppler evaluation of renal hemodynamic changes in essential hypertension[31]. Clinical application of these data is important in the evaluation of therapeutic effects of particular antihypertensive drugs. Calcium channel blockers were evaluated in several studies in regard to their influence on renal RI in EH[11,32]. There are no published studies about effects of valsartane on renal RI in EH.

RI enables assessment of renal vascular resistance that provides new hemodynamic parameter in the follow-up of patients with essential hypertension, as well as evaluation of effects of antihypertensive drugs on kidney.

This study has confirmed the hypothesis that RI in intrarenal arteries of patients with the newly established essential hypertension is higher than in healthy examinees. Significanlty higher Ris are observed already in patients with mild stage of hypertension, which confirms results of Galešić et al.[18,26]. Positive correlation of RI was demonstrated with creatinine clearance, left ventricular mass and age[18,33,34].

RI basically represents difference between peak systolic and enddiastolic velocity, and RI values may be the same in renal spectra of very different morphology, regardless of substantial differences in AT and AI. Since AT, AI and ESP were not studied in EH so far, we wanted to establish whether differences exist in AT and AI values, and presence of ESP in patients with EH compared to healthy subjects. We expected that the reduced compliance in hypertensive patients would cause decrease of AI, increase of AT, and smaller proportion of ESP presence in hypertensive patients as compared to healthy subjects. We actually assumed that analysis of multiple parameters of Doppler spectrum may provide more data than simple ratios of maximal and minimal velocities. ESP was present in smaller proprotion of hypertensive pa-

tients (85%) than in control examinees, but these slight differences have no significance in clinical practice; no changes in ESP presence were observed after the treatment. ESP can obviously not be used to evaluate efficacy of treatment with antihypertensives.

Like with RI values, this study demonstrated statistically significant differences in values of AI and AT between healthy examinees and patients with EH. AI is significantly higher in healthy examinees, while AT is significantly lower as compared to hypertensive patients. This confirms the hypothesis that reduced compliance in hypertensive patients reduces AI and prolongs AT.

After six-months of antihypertensive monotherapy significant reduction of RI was observed, as well as decrease of AT and increase of AI in comparison to these values prior to the treatment. AI values were significantly higher after treatment with both valsartane and niphedipine as compared to the values before therapy. AT values were also significantly lower after treatment with both drugs. The hypothesis was confirmed that antihypertensive treatment with both drugs results in the the reduction of RI, reduction of AT and increase of AI.

Both drugs significantly reduced systolic and diastolic blood pressure, with no significant difference in the degree of the reduction of systolic and diastolic BP values between two drugs.

Very important observation is that after six months of treatment RI values in patients treated with valsartane (RI=0.615±0.036) are significantly lower than RI values in patients treated with niphedipine (RI=0.642±0.030) ($p<0.01$). Although both drugs significantly reduced RI in interlobar arteries, valsartane had stronger effect in comparison to niphedipine, which demonstrates that vaslartane has better therapeutic effect on kidney than niphedipine, although there is no significant difference in two drugs in the degree of lowering systolic and diastolic blood pressure. Therefore the observed effect on RI may be independant on blood pressure.

Also, significant differences between patients treated with two drugs were demonstrated in AI values; valsartane treated patients had (AI=6.5±1.42) statistically significantly lower that patients treated with niphedipine (AI=5.7±1.55) ($p<0.03$). Like in the case of RI, these results indicate that vaslartane has better therapeutic effect on kidney that niphedipine. The lack of significant differences in AT values between patients treated with two drugs is most probably due to the fact that AT measurement is very dependant upon examiner, and errors in measurement are more pronounced than in AI or RI measurements. Latter two parameters are measured automatically after positioning of callipers, while in AI manual measurement of a very small distance is needed.

Apparently RI is the best Doppler parameter that indicates efficacy of a particular drug. AI may be used also, while AT measurements do not seem to be very useful.

Hypertension is responsible for important renal impairment in many patients, but the level of blood pressure is not a reliable predictor of the outcome of renal disease. Therefore it is hard to select patients with high risk for renal disease amnog many hypertensive patients. Microalbuminuria is a well known marker of subclinical impairment of organs and predictor of total cardiovascular mortality in patients with primary hypertension[35]. Some studies established correlation between microalbuminuria and increased RI in patients with essential hypertension who have impaired renal function[18,27,36]. Salveti demonstrated positive correlation of microalbuminuria and renal vascular resistance in hypertensive patients, since RI reflects renal vasoconstriction[37]. There are no studies about prognostic significance of increased renal RI. Leoncini demonstrated that lisinoprile was superior to niphedipine in the reduction of albuminuria and long-term reduction of RI[25]. They conclude that ACE inhibitors have better renoprotective effects.

One might conclude that the ideal renoprotective drug in addition to lowering of blood pressure has to increase perfusion of kidney by lowering of vascular resistance. Patients studied in this paper did not have microalbuminuria associated with hypertensive renal disease. Patients did not have left ventricular hypertrophy on ECG, or hypertensive changes of ocular fundus. Although relatively small number of patients was studied, we may speculate that changes of renal vascular resistance demonstrated by Doppler US represent earliest alterations that can be observed noninvasively, that may still be reversible. To confirm this hypothesis studies on large number of patients are needed.

There are several shortcomings for the routine clinical use of color duplex Doppler US for monitoring efficacy of therapy of essential hypertension with various medications. Primarilly these are very long examinations, that require very accurate measurements and examiners have to be very concentrated. Changes of all measured parameters are in a quite small range of only 10–15%, and accuracy in measurements is thus mandatory. Interlobar arteries have to be studied in three different parts of the kidney and optimal spectra have to be obtained. Mean value is calculated from all measurements. These time-consuming measuremnts are inconvenient for everyday clinical practice, and can be used only for research. Routinely for indications like diabetic nephropahty or ADPKD evaluation, RI is measured after the quick insonation of 2–3 arteries, after good spectra are obtained. But to evaluate effects of antihypertensive drugs on renal Doppler parametrs measurements have to be meticulous. The quality of results also depends considerably on the quality of the US scanner; in our opinion only high-end systems should be used for these studies, and these scanners are not very common in hospitals. Also, ultrasound is known to be operator dependant, and large »interobserver variability« exists between various examiners. In studies of this type it is advisable that all measurements are performed by only one well educated examiner.

In spite of all shortcomings, this study demonstrated that relatively simple Doppler parameter like resistance

index significantly correlates with all parameters studied, and reflects well the effects of antihypertensive medications for lowering of renal vascular resistance in essential hypertension. Additional Doppler parameters like AI, AT and ESP do not have a real significance in the assessment of efficacy of various antihypertensive drugs. Although AI was shown to have certain use in evaluation of efficacy of drugs, RI was better predictor than AI in regression analyisis. Therefore, RI seems to be sufficient among Doppler parameters to evaluate antihypertensive drugs effects on kidneys.

Conclusion

Renal RI is the best Doppler parameter to study therapeutic effects of antihypertensive monotherapy on kidney in essential hypertension. Doppler parameters other than RI seem not to have the practical clinical value. More favourable effect on renal vascular resistance (i.e. resistance index) of valsartane in comparison to niphedipine was demonstrated. Similar studies for assesing efficacy of other antihypertensive drugs may be conducted, using resistance index.

REFERENCES

1. LEWINGTON S, CLARKE R, QIZILBASH N, Lancet, 360 (2002) 1903. — 2. CHOBANIAN AV, BAKRIS GL, BLACK HR, Hypertension, 42 (2003) 1206. — 3. HAJJAR I, KOTCHEN TA, JAMA, 290 (2003) 199. — 4. KANNEL WB, Am J Manag Care, 8 (2002) 5. — 5. GO AS, CHERTOW GM, FAN D, N Engl J Med, 351 (2004) 1296. — 6. CIFKOVA R, ERDINE S, FAGARD R, J Hypertens, 21 (2003) 1779. — 7. BROOK RD, JULIUS S, Am J Hypertens, 13 (2000) 112. — 8. RUILOPE LM, MALACCO E, KHDER Y, KANDRA A, BÖNNER G, HEINTZ D, Clin Ther, 27 (2005) 578. — 9. SAITO I, SARUTA T, Hypertension Res, 29 (2006) 789. — 10. KAPLAN NM, Primary hypertension: Pathogenesis. In: KAPLAN NM (Ed) Kaplan's Clinical Hypertension (Lippincott, Phildaelphia, 2002). — 11. WILLIAMS GH, Hypertensive vascular disease. In: BRAUNWALD E (Ed) Harrison's Principles of Internal Medicine (McGraw-Hill, New York, 2001). — 12. COWLEY AW, ROMAN RJ, JAMA, 275 (1996) 1581. — 13. HELLMANN H, DAVIS JM, THURAU K, Kidney Int, 67 (1998) 211. — 14. BRKLJAČIĆ B, DRINKOVIĆ I, SABLJAR-MATOVINOVIĆ M, J Ultrasound Med, 13 (1994) 197. — 15. BRKLJAČIĆ B, CVITKOVIĆ-KUZMIĆ A, DMITROVIĆ R, RADOŠ M, VIDJAK V, Eur Radiol, 12 (2002) 2747. — 16. CARRETERO OA, OPARIL S, Circulation, 101 (2000) 329. — 17. BEEVERS G, LIP GYH, O'BRIEN E, BMJ, 322 (2001) 912. — 18. GALEŠIĆ K, BRKLJAČIĆ B, SABLJAR-MATOVINOVIĆ M, MOROVIĆ-VERGLES J, CVITKOVIĆ-KUZMIĆ A, BOŽIKOV V, Angiology, 51 (2000) 667. — 19. BRKLJAČIĆ B, MRZLJAK V, DRINKOVIĆ I, SOLDO D, SABLJAR-MATOVINOVIĆ M, HEBRANG A, Radiology, 192 (1994) 549. — 20. BRKLJAČIĆ B, SABLJAR-MATOVINOVIĆ M, PUTAREK K, SOLDO D, MOROVIĆ-VERGLES J, HAUSER M, Acta Radiologica, 38 (1997) 840. — 21. GALEŠIĆ K, SABLJAR-MATOVINOVIĆ M, TOMIĆ M, BRKLJAČIĆ B, Coll Antropol, 28 (2004) 667. — 22. COLEY BD, BRKLJAČIĆ B, Renal Failure and Transplantation. In: SLOVIS T (Ed) Caffey's Pediatric Diagnostic Imaging (Elsevier, Philadelphia, 2007). — 23. CVITKOVIĆ KUZMIĆ A, KOLAČEK S, BRKLJAČIĆ B, HUZJAK N, Pediatric Nephrology, 16 (2001) 371. — 24. BUDE RO, RUBIN JM, Radiology, 196 (1995) 612. — 25. LEONCINI G, MARTINOLI C, VIAZZI F, Nephron, 90 (2002) 169. — 26. GALEŠIĆ K, BRKLJAČIĆ B, BOŽIKOV V, DELIĆ-BRKLJAČIĆ D, Nephron, 80 (1998) 363. — 27. PONTREMOLI R, VIAZZI F, MARTINOLI C, Nephrol Dial Transplant, 14 (1999) 360. — 28. SLEIGHT P, Renin Angiotensin Aldosterone Syst, 1 (2000) 18. — 29. GOSSE P, Vasc Health Risk Manag, 2 (2006) 195. — 30. WAGSTAFF AJ, Drugs, 66 (2006) 1881. — 31. KREMKAU WF, Diagnostic ultrasound: principles and instruments (W.B. Saunders, Philadelphia, 2001). — 32. AKUZAWA N, KADAMURA T, KURASHINA T, Am J Hypertens, 11 (1998) 697. — 33. ALTERINI B, MORI F, TERZANI E, Ann Ital Med, 11 (1996) 107. — 34. VEGLIO F, MAURO F, REMO M, Kidney Int, 48 (1995) 1611. — 35. BIANCHI S, BIGAZZI R, CAMPESE VM, Am J Kidney Dis, 34 (1999) 973. — 36. JAGER A, KOSTENCE PJ, RUHE HG, Arterioscler Thromb Vasc Biol, 19 (1999) 617. — 37. MATTEI F, ARZILLI F, GIOVANETTI R, PENNO G, ARRIGHI S, SALVETTI A, Eur J Clin Invest, 27 (1997) 755.

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UTJECAJ ATII BLOKATORA I BLOKATORA KALCIJSKIH KANALA NA BUBREŽNI KRVOŽILNI OTPOR U BOLESNIKA S ESENCIJALNOM HIPERTENZIJOM

SAŽETAK

Dopler je koristan u procjeni bubrežnog krvožilnog otpora, a indeks otpora (RI) korelira značajno s krvnim tlakom i funkcijom bubrega u brojnim patološkim stanjima. Cilj je izmjeriti i usporediti bubrežne doplerske indekse kod bolesnika s novodijagnosticiranom esencijalnom hipertenzijom (EH) i zdravih osoba; odrediti promjene doplerskih indeksa u bolesnika nakon šestomjesečne monoterapije ili AT II blokatorom (valsartan) ili blokatorom kalcijskih kanala (nifedipin); odrediti koji lijek ima bolji renoprotektivni učinak. Pregledano je 65 zdravih osoba i 69 bolesnika s novodijagnosticiranom EH bez znakova oštećenja ciljnih organa. Dupleks dopler ultrazvukom intrarenalnih interlobarnih arterija izmjereni su RI, akceleracijski indeks (AI) i akceleracijsko vrijeme (AT). Antihipertenzivna monoterapija je provedena valsartanom u 34 bolesnika, a nifedipinom u 35 bolesnika. Dopler je ponovljen nakon provedene šestomjesečne terapije. RI u bolesnika s prvim stadijem EH je značajno viši u usporedbi sa zdravim ispitanicima ($p<0,001$), a

značajno niži u usporedbi s drugim stadijem EH ($p<0,001$). Značajan pad sistoličkog ($p<0,001$) i dijastoličkog krvnog tlaka (KT) ($p<0,001$) je uočen nakon liječenja. RI u zdravih ispitanika ($RI=0,59\pm0,023$) je značajno niži nego kod EH ($RI=0,66\pm0,26$) ($p<0,001$), dok je AI značajno viši ($p<0,001$), a AT značajno niže ($p<0,001$). U bolesnika liječenih i valsartanom i nifedipinom vrijednosti RI su značajno niže nego prije liječenja ($p<0,001$), vrijednosti AI su značajno više, a AT značajno niže, i to nakon liječenja s oba lijeka. RI nakon liječenja kod bolesnika liječenih valsartanom ($RI=0,615\pm0,036$) je značajno niži od RI kod bolesnika liječenih nifedipinom ($RI=0,642\pm0,030$) ($p<0,01$). Regresijska analiza za prediktivne vrijednosti RI, AT, AI u odnosu na dobno-standardizirani sistolički i dijastolički KT zdravih ispitanika i hipertoničara pokazala je da je RI najjači i statistički značajan prediktor u svim skupinama ispitanika. Šestomjesečna monoterapija EH valsartanom ili nifedipinom je jednako djelotvorna u smanjenju krvnog tlaka, ali valsartan ima bolje djelovanje na bubreg. Indeks otpora u intrarenalnim arterijama je najbolji parametar doplerskog spektra u procjeni djelovanja antihipertenziva na bubreg.