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The analysis of office and daily hemodynamics parameters and pharmacological therapy features in patients with chronic kidney disease and arterial hypertension

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Objective. *To study the effect of antihypertensive, lipid-lowering and metabolic therapy on office and daily hemodynamic parameters, central aortic blood pressure, vascular wall stiffness and life quality in patients with or without 1–2 grade of arterial hypertension (AH).*

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Materials and methods. *We examined patients with 1–2 grade of arterial hypertension (AH) and 3 stage of CKD. Hemodynamic parameters were assessed using daily monitor of arterial pressure «BPLab». Life quality was determined using the MOS SF36 questionnaire.*

Results. *Patients with AH and CKD had the most significant changes in central hemodynamics and vascular wall stiffness.*

Conclusion. *The combination of antihypertensive therapy (losartan and diltiazem) with meldonium and rosuvastatin significantly reduced central and peripheral hemodynamics and vascular stiffness parameters. Meldonium, added to standard therapy, significantly improves patient's life quality.*

Key words: *arterial hypertension, chronic kidney disease, central aortic blood pressure, vascular wall stiffness, daily monitoring.*

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Introduction

BP control reduces cardiovascular risk and include not only blood pressure (BP) level correction, but also all modifiable risk factors, prevents or treats target organ damage and associated clinical conditions.

Kidney damage in patients with arterial hypertension (AH) has been studied by many researchers over the last years [1,2]. It has been proven that chronic kidney disease (CKD) is associated with AH, chronic heart failure (CHF), and diabetes mellitus [3–5]. However, the association between CKD and 1–2 grade AH in young patients as well as the factors affecting the development of CKD have not been studied enough yet.

The effect of various antihypertensive therapy (AHT) on the outcomes was assessed using central aortic pressure (CAP) and wave reflection index (augmentation index — AIx) over the last years [5–10]. Antihypertensive medications affect pulse wave and central hemodynamics parameters differently, despite the same brachial artery BP reduction [9,13].

Objective

To study the effect of antihypertensive, lipid-lowering and metabolic therapy on office and daily hemodynamic parameters, central aortic blood pressure (CAP), vascular wall stiffness and life quality (LQ) in patients with or without 1st or 2d grade AH.

Materials and methods

Our study included patients from the Department of Nephrology and the Department of Cardiology of Kabardino-Balkar State University named after H M Berbekov of Kabardino-Balkar Republic and ambulatory patients from Nalchik city clinics. Group 1 inclusion criteria were: the presence of stage 3 CKD (estimated glomerular filtration rate (eGFR) 30–60 ml/min)) in combination with 1st or 2d grade AH, age from 45 to 72 years, duration of AH less than 10 years lack of regular AHT. Group 2 inclusion criteria were: the presence of 1st or 2d grade AH, age from 45 to 72 years, the duration of AH less than 10 years, lack of regular AHT. Group 3 inclusion criteria were: the presence of stage 3 CKD (eGFR 30–60 ml/min), age from 45 to 72 years. The control group included healthy patients according to examination (general clinical examination, biochemical blood test, special (questioning), statistical, as well as comparative and system analysis methods)).

The first group included 45 patients with stage 3 CKD (eGFR 30–60 ml / min) in combination with 1st or 2d degree AH (average age 60±9 years) — 19 men and 26 women. The second group included 45 patients with 1st or 2d grade AH and without CKD. The third group included 45 patients with stage 3 CKD without AH. The fourth (control) group included 30 clinically healthy participants. All the groups were comparable by age and gender.

Office and daily hemodynamic parameters and daily average CAP parameters were measured using the BPLab daily blood pressure monitor with BPLab Vasotens and BPLab Vasotens-office software from Petr Telegin (Russia) before treatment and 8 weeks after.

LQ was assessed using MOS SF36 questionnaire before and 8 weeks after the treatment. The questionnaire included the following parameters: physical health: physical activity, physical functioning, bodily

pain and general health; mental health: vitality, social activity, emotional functioning, as well as a comparison of patients' well-being.

Statistical analysis of obtained data was performed using Statistica 10.0 software. We calculated the arithmetic mean and standard deviations of the parameters and representativeness errors. Normal distribution of obtained data was presented as M±m, where M is the arithmetic mean of studied parameters, m — representativeness error. The significance of differences between groups was assessed using Student's t-test. A p value less than 0.05 was considered significant.

Table 2. **Pharmacological therapy received by participants**

Group	Received therapy
1 (CKD III+AH), n=45	1. Losartan 100 mg at 8 a. m. 2. Diltiazem 180 mg once a day 3. Rosuvastatin 10 mg at 8 p.m. 4. Meldonium 500 mg 2 times a day at 8 a.m. and 2 p.m.
2 (AH), n=45	1. Losartan 100 mg at 8 a. m. 2. Diltiazem 180 mg once a day 3. Rosuvastatin 10 mg at 8 p.m. 4. Meldonium 500 mg 2 times a day at 8 a.m. and 2 p.m.
3 (CKD III), n=45	1. Rosuvastatin 10 mg at 8 p.m. 2. Meldonium 500 mg 2 times a day at 8 a.m. and 2 p.m.

Results

Clinical characteristics of patients and received therapy are presented in tables 1 and 2, respectively.

The results of the office hemodynamic parameters monitoring before and after the treatment are presented in table 3.

The results of the study show that initial office hemodynamic parameters were higher compared with average daily parameters in all the participants. Office hemodynamic and vascular wall stiffness parameters (arm and ankle SBP, DBP, average daily BP, pulse pressure (PP), heart rate (HR), pulse transit time (PTT), aortic pulse wave velocity (PWVao), augmentation index (AIx), BP rise rate (dPdt), systolic area index (Ssy), cardio-ankle vascular index (CAVIa)) changed significantly in patients with CKD and AH (table 3).

Reference parameters changed less in patients with CKD without AH. It is also remarkable that patients from this group had increased office hemodynamic and vascular wall stiffness parameters: arm SBP, ankle SBP, DBP, average aortic BP, PP, PTT, PWVao, AIx, dPdt, Ssy, CAVIa, as well as CAP param-

Table 1. **Clinical and demographical characteristics of participants**

Parameter	Group 1 (CKD III+AH) n=45	Group 2 (AH) n=45	Group 3 (CKD III) n=45	Group 4 (healthy) n=30
Average age, years	60±9	62±10	60±9	59±11
Men, n (%)	19 (42)	22 (49)	20 (44)	14 (46)
Women, n (%)	26 (58)	23 (51)	25 (56)	16 (54)
Smokers, n (%)	11 (24)*	11 (24)*	12 (27)*	0 (0)
AH, n (%)	45 (100)*	45 (100)*	0 (0)	0 (0)
1st grade AH, n (%)	20 (44)*	21 (47)*	0 (0)	0 (0)
2d grade AH, n (%)	25 (56)*	24 (53)*	0 (0)	0 (0)
CHF (1–2 FC according to NYHA), n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Potassium, mEq/l	4.8±0.85**	4.8±0.57*	4.9±0.88**	4.2±0.44
Sodium, mEq/l	143±3.29	136±3.35	142±2.84	138±3.12
Uric Acid, μmol/L	444±89	342±85	374±87	272±91
Hemoglobin blood level, g/l	137±23	138±16	136±24	137±15
Hematocrit, %	38.94±5.83	41.83±5.14	39.48±6.60	41.18±4.16
Creatinine blood level, mg/dl	1.47±0.43*	0.88±0.11	1.38±0.37*	0.73±0.17
Serum albumin level, g/l	37±6.4	41±5.1	39±5.5	42±5.4
Albuminuria, mg/day	8.4±3.1*	3.46±0.7	7.3±2.7*	3.08± 0.7
Left ventricular hypertrophy, n (%)	10 (22)*	8 (18)*	0 (0)	0 (0)
GFR according to CKD-EPI, ml/min/1.73 м^2	47.5±11.1**	75.4±7.5	45.9±11.7**	106.8±14.5
CHA2DS2-VASc score	5±1*	3±1	2±1	2±1
Hyperlipidemia, n (%)	45 (100) *	45 (100)*	45 (100)*	0 (0)
Total cholesterol, mmol/l	5.84±0.9*	5.91±0.8*	5.92±1.0*	3.8±0.5
Low-density lipoprotein level, mmol/l	3.323±0.6	3.05±0.7	3.24±0.6	2.1±0.6
High-density lipoprotein level, mmol/l	1.1±0.5	1.2±0.6	1.1±0.5	1.9±0.4
Triglycerides, mmol/l	1.6±0.6	1.7±0.6	1.6±0.5	1.9±1.2

* p<0,05, **p<0,01, *** p<0,001, compared with the control group.

Table 3. **The dynamics of office hemodynamic parameters during combinative treatment**

Parameter		Group 1 (CKD III+AH) n=45	Group 2 (AH) n=45	Group 3 (CKD III) n=45	Group 4 (healthy) n=30
SBP, mmHg (arm)	Initially	152.3±5.72***	148.4±4.24**	132.1±5.47*	113.4±3.52
	After treatment	134.2 ±4.82*#	129.5± 4.25*#	124.2±2.63	
SBP, mmHg, (ankle)	Initially	179.8±4.57***	168.3±3.59***	153.5±4.11*	141.7±3.47
	After treatment	159.5±4.06*##	153.6±3.94*#	148.6±3.73	
DBP, mmHg	Initially	89.2±3.83**	85.8±3.73*	78.4±2.92*	70.2±3.27
	After treatment	78±2.73*#	73±3.04#	71.2±2.74	
Average BP, mm Hg	Initially	139.6±4.91**	136.4±2.53**	124.7±2.22*	110.5±2.82
	After treatment	121.4±2.01*##	116.8±2.81##	121.1±3.02	
PP, mmHg	Initially	72.3±4.74**	68.6±3.53**	48±2.35*	39±3.23
	After treatment	52.5±2.63*##	47.2±2.92##	43.8±2.19	
HR, beats per minute	Initially	82.4±3.13**	76.5±2.89*	71.6±2.32	69±2.04
	After treatment	76.2±2.04*#	74.6±2.15	70.2±1.96	
PTT, ms	Initially	159.3±4.63***	149±4.74***	131.1±3.18**	117.7±2.74
	After treatment	132.8±3.83*##	123.8±3.25###	120.2±2.93#	
PWVao, ms	Initially	19.2±1.92**	17.5±1.77**	12.3±1.41*	7.2±1.82
	After treatment	10.3±1.81##	9.6±1.64#	8.8±1.5	
AIx, %	Initially	44.7±4.73***	38.5±3.26**	28.8±3.69*	18.5±2.83
	After treatment	25.2±3.92##	23.6±3.51##	21.7±3.12	
dPdt, mm Hg/s	Initially	1090.74±92.14***	892.85±69.95***	525.52±45.25**	336.46±22.36
	After treatment	809.75±68.15***#	683.58±55.27**#	425.24±53.41#	
Ssy, mm Hg	Initially	25.3 ± 2.52***	19.7 ± 1.51***	9.21 ± 1.08*	4.9 ± 1.7
	After treatment	9.2 ± 2.25##	7.8 ± 1.14##	5.8 ± 1.13#	
CAVIa	Initially	28.19±2.36***	26.11±2.02**	23.4±2.43*	15.2±1.47
		24.62±1.74*#	22.93±2.61*	18.3±1.62	

* The differences are significant compared with the control group (p<0,05), ** p<0,01, *** p<0,001;
# The differences are significant compared with the initial paraments (p<0,05); ## — p<0,01, ### — p<0,001.

eters (aortic SBP, average aortic BP, aortic PP, aortic AIx (table 4)).

The most significant differences in CAP (aortic SBP, Average aortic BP, aortic PP, aortic AIx) were registered in patients with CKD and AH, when analyzing daily central hemodynamic parameters (table 4).

Patients with CKD without AH initially had significant increase of some central hemodynamic parameters, such as aortic SBP, aortic PP, aortic AIx (table 4).

Central and peripheral hemodynamic parameters significantly decreased in patients from group 1 and 2

Table 4. **The dynamics of daily CAP parameters during combinative treatment**

CAP parameters	Group 1 (CKD III+AH) n=45	Group 2 (AH) n=45	Group 3 (CKD III) n=45	Group 4 (healthy) n=30
Aortic SBP, mmHg — before/after treatment	139.6±5.29*/ 121.5±2.23##	135.9±2.22*/ 117.5±2.64###	125.1±2.23*/ 120.9±3.17	110.4±2.37
Aortic DBP, mmHg — before/after treatment	81.7±3.82*/ 73.4±1.73#	79.3±1.70*/ 72.5±1.12##	76.4±1.78/ 75.8±1.35	73.1±0.78
Aortic average BP, mmHg — before/after treatment	105.8±5.73**/ 88.5±1.69##	100.1±3.45*/ 84.3±2.37##	86.4±2.35/ 85.7±1.89	83.4±1.12
Central arterial pulse pressure (aortic PP), mmHg — before/ after treatment	67.3±4.09***/ 44.7±1.61###	60.7±3.65***/ 41.3±1.92###	45.3±1.68*/ 40.9±1.16#	37.7±1.36
Aortic AIx (AIxao), % before/after treatment	36.6±4.41***/ 20.2±2.13##	27.7±3.52**/ 19.4±1.65#	23.3±2.09*/ 20.3±2.15	16.1±1.22
Aortic AIx (AIxao), % reduced to HR =75 beats per minute before/ after treatment	32.6±4.44**/ 21.2±2.72#	27.4±3.21**/ 20.7±3.62#	23.2±2.06*/ 21.3±2.76	17.6±1.86

* The differences are significant compared with the control group (p<0,05), ** p<0,01, *** p<0,001; # The differences are significant compared with the initial paraments (p<0,05); ## — p<0,01, ### — p<0,001.

during combined antihypertensive, lipid-lowering and metabolic therapy (table 3, 4).

Office hemodynamic and vascular wall stiffness parameters decreased (arm SBP, ankle SBP, DBP, PP, PTT, PWVao, AIx, dPdt, Ssy, CAVIa) and CAP parameters increased (aortic SBP, aortic PP, aortic AIx) (table 3, 4) in patients with CKD without AH (group 3) during antihypertensive and lipid-lowering therapy (meldonium and rosuvastatin, respectively). But the changes were significant only by PTT, dPdt, SsY (table 3) and by aortic PP (table 4) parameters.

LQ parameters between groups were initially comparable. The analysis LQ parameters revealed reliable, statistically significant improvement of the following parameters in patients from groups 1 and 2: physical functioning, vitality, social functioning, emotional functioning, mental health, as well as health psychological component (Figure 1a, 1b).

Physical health parameters significantly improved in patients from group 3, when changes in psychological health parameters were insignificant (Figure 1c).

The best dynamics in LQ parameters were registered in patients from groups 1 and 2 who received AHT and 1000 mg of meldonium per day (Figure 1a and 1b).

Discussion

This study represents features of antihypertensive, lipid-lowering, and metabolic therapy effects on the office and average daily hemodynamic parameters, CAP parameters, vascular wall stiffness and LQ in patients with CKD and AH.

The prognostic significance of CAP and arterial stiffness can be proven by their inclusion into the latest European guidelines on AH (2018) as target organ damage signs [1].

The results of the study showed that the greatest hemodynamics and vascular stiffness parameters increase were observed in patients with CKD and AH.

The smallest changes of reference parameters in patients with CKD without AH, the initial increase in office hemodynamics and vascular stiffness, as well as daily CAP parameters indicate cardiorenal association, which can be presented not only as morphofunctional impairment of renal regulation, but also as hemodynamic and arterial endothelial dysfunction, for example arterial stiffness.

The results of this study reinforce recent studies that have shown an independent inverse correlation between GFR <60 ml/min /1.73 m^2 and the number of cardiovascular events. It is also remarkable that CVD occur in patients with renal dysfunction 64 % more often compared with patients with preserved function, and cardiovascular mortality — by 22–35 % [2, 11, 12].

The results of the Chronic Kidney Disease Prognosis Consortium study, which involved over 1 million patients in general population with high-risk and CKD, showed independent from each other and from main cardiovascular risk factors inverse with GFR and direct with albuminuria correlation with general and cardiovascular mortality and with renal outcomes [2].

Thus, further studies on the correlation between central hemodynamic parameters, arterial stiffness and daily blood pressure monitoring in patients with CKD, AH and dyslipidemia are needed.

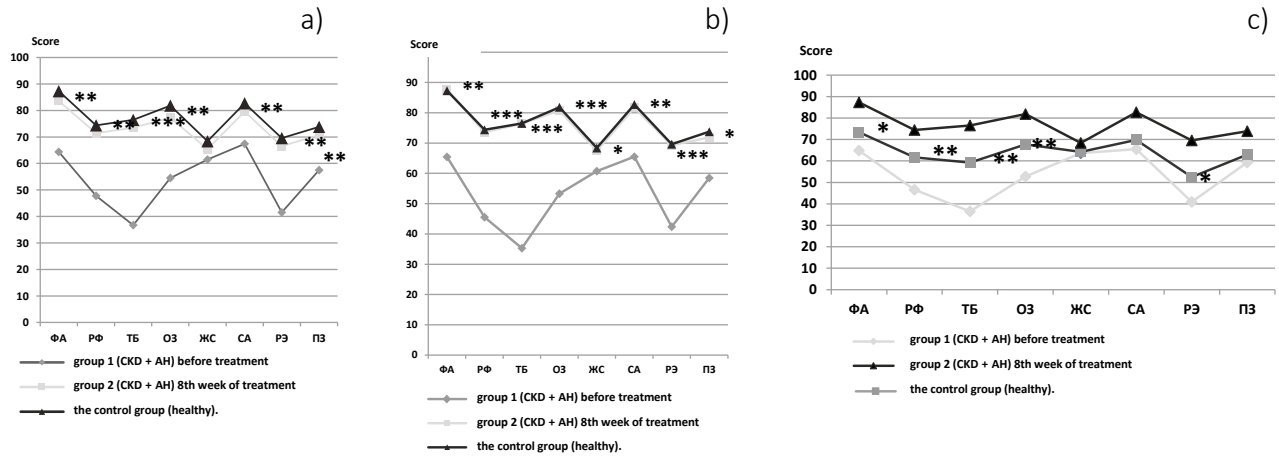

Figure 1. The dynamics of LQ parameters in patients from group 1 (a), group 2 (b) and group 3 (c) during treatment
a) * The differences are significant compared with the control group (p<0,05), ** p<0,01, *** p<0,001; # The differences are significant compared with the initial paraments (p<0,05); ## p<0,01, ### p<0,001.
b) ** The differences are statistically significant compared with the initial paraments p<0,05,** p<0,01, *** p<0,001.

Conclusion

Thus, all the patients had higher initial hemodynamic parameters compared with daily parameters. Patients with stage 3 CKD had increased central and peripheral hemodynamic parameters according to daily BP monitoring. Patients with stage 3 CKD and AH had increased office hemodynamic and CAP parameters, arterial stiffness and decreased arterial elasticity.

The combination of antihypertensive therapy (losartan and diltiazem) with meldonium and rosuvastatin significantly reduced central and peripheral hemodynamics and vascular stiffness parameters in patients with stage 3 CKD and AH. Patients with 1 and 2 grade AH as well as with stage 3 CKD with AH, who received 1000 mg meldonium per day, added to standard therapy, had significant life quality improvement.

Conflict of interest: None declared.

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