International Journal of Biomedicine 5(4) (2015) 203-206
doi: 10.21103/Article5(4)_OA7

ORIGINAL ARTICLE

Cardiology

INTERNATIONAL JOURNAL OF BIOMEDICINE

Effectiveness of Personalized Therapy in Elderly Patients with Isolated Systolic Hypertension

E.A. Kartashova, PhD[1]; I.V. Sarvilina, PhD, ScD[2]

[1]*Rostov-on-Don State Medical University*
[2]*Medical Centre "Novomeditsina"*
Rostov-on-Don, the Russian Federation

Abstract

The purpose of this study was the development of personalized modes of therapy in elderly patients with isolated systolic hypertension (ISH).

The study included 306 persons divided into two groups: Group 1 (Control) included 150 elderly persons without arterial hypertension (AH), and Group 2 included 256 elderly patients (early old-age pension, between 65 and 74 years) with ISH (ESH/ESC,2013) according to the inclusion/exclusion criteria. All patients of Group 2 were divided into three subgroups depending on the combination of drugs at the beginning of the study. Group 2a (n=53) received amlodipine (5 mg/day) and indapamide-retard (1.5 mg/day), Group 2b (n=53) received valsartan (80 mg/day) and indapamide-retard (1.5 mg/day), and Group 2c (n=50) received amlodipine (5 mg/day) and valsartan (80 mg/day). The duration of therapy was 5.2 years.

At the stage of data collection and screening, we applied standard methods for identification of ISH and secondary hypertension. Molecular phenotyping of blood serum was performed with methods of proteomics. We obtained the data of the molecular interactions and functional features of proteins from the STRING 10.0 database.

Proteomic analysis contributes to the development of a personalized mode treatment in ISH patients, which is the safest and most efficient: 135 ISH patients switched to the administration of the amlodipine+valsartan combination. **(Int J Biomed. 2015;5(4):203-206.)**

Keywords: *isolated systolic hypertension; personalized therapy; proteomics; bioinformatics; molecular interactions*.

Introduction

The purpose of this study was the development of personalized modes of therapy in elderly patients with isolated systolic hypertension (ISH).

Currently, arterial hypertension (AH) is often defined as accelerated aging. Aging has a pronounced effect on the cardiovascular system, largely involving vessels (vascular aging). Aging is associated with the development of the remodeling processes in the cardiovascular system [1-3]. Experimental and clinical trials have shown that myocardial contractility and stiffness of vascular walls are vulnerable to age-related changes [3]. A molecular map of aging in the cardiovascular system of elderly patients, accompanied by the emergence of AH, cannot be described only on the basis of standard methods of clinical research.

***Corresponding author**: Irina V. Sarvilina, PhD, ScD. CEO of Medical Centre «Novomeditsina», Rostov-on-Don, Russian Federation..E-mail: isarvilina@mail.ru*

Modern methods and technologies of molecular analysis of large interactomes (blood, urine) and human tissues (myocardium, vascular wall)—including methods of genomics, transcriptomics, proteomics, and metabolomics—allow us to explore pathways of aging of target organs in elderly AH patients.

According to multicenter studies, modern hypotensive drugs indirectly eliminate remodeling processes in the myocardium and vascular walls, mainly by reducing systolic and diastolic blood pressure (BP). Today we need progress in the development and clinical application of the hypotensive drugs which impact key genomic-epigenomic interactions underlying the aging processes of the cardiovascular system, taking into account the results of population studies.

Materials and Methods

To address this need, we conducted a comparative prospective cohort study with parallel design. The study included 306 persons divided into two groups: Group 1

(Control) included 150 elderly persons without AH, and Group 2 included 256 elderly patients (early old-age pension, between 65 and 74 years) with ISH, according to the inclusion/exclusion criteria. Patients with ISH corresponded to the criteria for the classification of BP levels (SBP>140 mmHg and DBP<90 mmHg) and risk stratification – middle (n=87) and high (n=69) additional risk proposed by the ESH/ESC (2013) Guidelines for the management of arterial hypertension [4]. ISH duration was 13.5 years. All patients of Group 2 were divided into three subgroups depending on the combination of drugs [(amlodipine (calcium antagonist), indapamide-retard (diuretic), and valsartan (angiotensin receptor blocker)] at the beginning of the study.

Group 2a (n=53) received amlodipine (5mg/day) and indapamide-retard (1.5mg/day), Group 2b (n=53) received valsartan (80mg/day) and indapamide-retard (1.5mg/day), and Group 2c (n=50) received amlodipine (5mg/day) and valsartan (80mg/day). The duration of therapy was 5.2 years. The subgroups were matched for age, sex, SIH Grades, middle/high additional risk stratification, and disease duration. The antihypertensive efficacy of different treatment regimes was evaluated by the BP decrease (more than 15%) and achievement of target BP.

At the stage of data collection and screening, we applied standard methods for identification of ISH and secondary hypertension: the assessment of the patient`s complaints, medical history, physical examination, 24-hour ABPM, ECG (ATES MEDICA, Italy-Russia), echocardiography (Samsung-Medison, South Korea), blood and urine tests, biochemical analysis of blood and urine, blood level of aldosterone and corticosteroids, plasma renin activity, urinary catecholamines and metabolites (ELISA, Siemens 2000, Germany), coagulogram («Instrumentation Laboratory», USA), and an MRI of adrenal glands, kidney and brain (Philips Intera 1.5T, Japan).

Molecular phenotyping of blood serum was performed with methods of proteomics: the prefractionation, the separation of proteins with standard sets (MB-HIC C8 Kit, MB-IMAC Cu, MB-Wax Kit, «Bruker», USA), and the matrix-assisted, laser desorption-ionization, time-of-flight mass spectrometry (MALDI-TOF-MS/MS, Ultraflex II, «Bruker», USA). The partially identified sequences were then submitted to "BLAST protein-protein" and screened against the *Homo sapiens* Swissprot database to check whether this identification matched the MASCOT-identification (Matrix Science). We obtained the data of the molecular interactions and functional features of proteins from the STRING 10.0 database.

Based on the data of standard methods of identification of ISAH and molecular phenotyping of blood serum, we conducted a personalized selection of hypotensive drug therapy for each patient. After 3 years of personalized hypotensive drug therapy, parameters of standard methods and molecular phenotyping of blood serum were measured.

The study was conducted in accordance with ethical principles of the Declaration of Helsinki and approved by the Rostov-on-Don State Medical University Ethics Committee. Written informed consent was obtained from each patient.

Statistical analysis was performed using the statistical software «Statistica 12.0». A probability value of $P<0.05$ was considered statistically significant.

Results

Among Group 2 patients, Grade 1(n=48), Grade 2(n=82), and Grade 3(n=26) of SIH were identified (Table 1). MRI signs of leukoaraiosis were detected in all patients with ISAH.

Table 1.

Clinical and anamnestic characteristics of ISH patients

Parameter	Group 2a (n=53)	Group 2b (n=53)	Group 2c (n=50)
Sex (male/female), n	34/19	33/20	27/23
Age, years	69.2±2.9	67.3±2.5	68.2±2.8
Weight, kg	66.7±1.3	69.4±1.6	68.5±1.5
Height, cm	170.3±1.9	167.5±1.3	169.5±1.5
BMI, kg/m^2	19.6±1.2	20.8±1.3	22.0±1.5
Duration of disease, years	12.3±1.5	15.7±1.9	14.2±1.8
Hypertensive crises, n	16	11	7
Risk factors:			
Heredity			
AH	34	34	35
CHD	34	34	35
Dyslipoproteinemia	34	34	35
Anamnesis			
CVD	25	27	25
Dyslipoproteinemia	34	34	35
Smoking	11	8	10
Poor nutrition	22	13	17
Obesity	-	-	-
Low physical activity	25	23	25
Target organs and associated clinical conditions:			
Brain and eyes (headache, dizziness, impairment of view, speech, TIA, sensory and motor disorders)	34	34	35
Heart (heartbeat, pain in the chest, shortness of breath, swelling)	34	34	35
Kidney (thirst, polyuria, nocturia, hematuria, swelling)	4	5	5
Peripheral arteries (cold extremities, intermittent claudication)	5	8	7
Physical examination:			
Vascular changes in the fundus	34	34	35
Heart (offset heart borders, arrhythmia, CHF)	34	34	35
Peripheral arteries (pulse weakening or disappearance, asymmetrical radial pulse, cold extremities, symptoms of skin ischemia)	8	13	9
Carotid arteries (systolic murmur)	9	12	10
ECG data:			
Sokolov – Lyon index (SV1+RV5-6)>3.5mV, n	34	34	35
Cornell voltage QRS duration product (>244 mV*ms), n	34	34	35

BMI–body mass index, CHD – coronary heart disease; TIA – transient ischemic attack; CHF – chronic heart failure.

At the stage of data collection and screening, we detected intergroup differences between indicators of 24-h daytime and nighttime SBP and DBP and heart rate in ISH patients taking 3 modes of hypotensive therapy. We revealed a significant reduction of these parameters in Group 2c compared to similar indicators in Groups 2a and 2b.

Daytime SBP: 141.2±3.4mmHg (2a), 138.3±3.6mmHg (2b), and 117.6±3.5mmHg (2c), *P2a/2c<0.001, P2b/2c<0.001*;

Daytime DBP: 78.4±1.6mmHg (2a), 73.5±1.3mmHg (2b), and 69.4±2.4mmHg (2c), *P2a/2c<0.001, P2b/2c<0.01*;

Nighttime SBP: 130.9±3.6mmHg (2a), 127.4±3.2mmHg (2b), and 117.6±2.9mmHg (2c), *P2a/2c<0.001, P2b/2c<0.001*;

Nighttime DBP: 81.8±1.4mmHg (2a), 75.4±1.2mmHg (2b), and 67.6±1.8mmHg (2c), *P2a/2c<0.001, P2b/2c<0.01*;

Heart rate: 84.5±1.5bpm (2a), 77.2±1.8bpm (2b), and 72.3±1.2bpm (2c), *P2a/2c<0.001, P2b/2c<0.01*.

The downward trend of LVMI [139.5±4.7g/m^2 (2a), 137.3±4.3g/m^2 (2b), and 129,4±3,9g/m^2 (2c), P2a/2c<0.001, P2b/2c<0.05] was observed in patients taking the combination of amlodipine and valsartan.

Proteomic analysis helped in the detection of differences in the component composition of the serum proteins in ISH patients with varying grades who were taking different modes of hypotensive therapy, compared to Group 1 (Table 2).

Proteomic analysis contributes to the development of a personalized mode treatment in ISH patients, which is the safest and most efficient: 135 ISH patients switched to the administration of the amlodipine+valsartan combination. After 3 years of personalized hypotensive drug therapy, we identified a significant decrease in parameters of daytime/nighttime SBP and DBP, daily indexes, heart rate and of the myocardial performance index, as well as signs of the progression of ischemic, distrophic, metabolic, and morphogenetic disorders in the cardiovascular system in accordance with changes of peptide indicators in patients of Group 2c.

Bioinformatics analysis revealed the presence of molecules that are the participants in the universal pathways of cardivascular aging and the molecular interactions involved.

Discussion

Proteomic analysis revealed an increase in the absolute number of ISH patients with an abnormal profile of serum proteins performing certain biological functions and having various localizations in the intra- and extracellular spaces (Table 2). Molecules interact among themselves and with other molecules as participants in universal pathways in cardivascular aging in ISH patients: RAAS (renin-

Table 2

Qualitative profile of serum proteins in elderly ISH patients and control group

№	Protein name	Number of patients with the expression of the serum protein (n)							MW* (Da)	Functional process (sources: InterPro, Entrez, SWISS-PROT, NRDB, , PDB, KEGG)
		Control (n=150)	Gr. 2a (n=53)	Gr. 2a[1] (n=11)	Gr. 2b (n=53)	Gr. 2b[2] (n=10)	Gr. 2c (n=50)	Gr. 2c[3] (n=135)		
1	Disheveled-associated activator of morphogenesis 1	23	53	8	53	7	50	28	123396	Epidermal cell proliferation, and glucose and lipid metabolism
2	Apolipoprotein D	138	12	3	15	2	35	114	21262	Fatty acid and steroid metabolism
3	Brain spectrin	144	22	6	19	7	34	108	41404	Cytoskeletal protein, neurotransmission, neuromuscular junction
4	Myocardial ischemic preconditioning upregulated protein 1	137	34	4	37	4	44	103	56904	Nuclear factor, cell apoptosis, the gene expression of downstream inflammatory mediators
5	Neprilysin	10	22	10	23	8	27	14	85460	Amyloid beta regulation, the regulation of signaling peptides
6	Gamma butyrobetaine hydroxylase	145	22	3	33	6	45	130	44687	L-carnitine biosynthesis pathway, mitochondrial beta oxidation
7	Endothelial growth factor A	142	32	4	35	7	44	132	27042	Vasculogenesis, neovascular age-related macular degeneration
8	Angiotensin-converting enzyme	4	14	3	10	3	10	2	149715	The convertion of vasoactive peptides
9	Angiotensinogen	3	12	3	9	3	10	1	53154	Blood pressure, body fluid and electrolyte homeostasis
10	Hypoxia inducible factor 1	129	23	7	34	8	42	132	92670	Transcription factor, regulator the hypoxia in cells
11	Peroxisome proliferator-activated receptors D	125	28	6	34	9	40	127	49903	Nuclear hormone receptor, integrator of transcription repression and nuclear receptor signaling
12	Voltage-dependent calcium channels 1D and 1C	26	29	5	32	7	22	47	245141	The regulator of hormone and neurotransmitter release, muscle contraction, cellular functions
13	Nitric oxide synthase, endothelial	147	39	5	41	9	45	132	133289	Vascular tone, cellular proliferation, leukocyte adhesion, platelet aggregation
14	Endothelin I	4	42	7	38	8	31	35	24425	Vasoconstrictor, vascular homeostasis

MW* – molecular weight (Da); Groop 2a[1], Group 2b[2], Group 2c[3] - after 3 years of personalized hypotensive drug therapy

angiotensin-aldosterone system), PPARs, WNT (Wg/Int), NOTCH signaling pathways, mitochondria and ROS signaling pathways (electron-transport chain signaling, stress-induced protein kinases: JNK and MST-1), and genome surveillance pathways (tumor suppressors and antagonistic pleiotropy).

Each protein molecule in the functional group interacts with other protein molecules. For example, the molecular interactions of hypoxia inducible factor 1, alpha subunit (HIF-1alpha) are presented in Fig.1. Serum HIF-1alpha concentration rose in ISH patients, and was most pronounced in Group 2c.

Conclusion

We identified potentially new biomarkers of cardiovascular aging that could help in developing a noninvasive, serum-based diagnostic test. This study is the first step in the development of a new system for creation of personalized hypotensive therapy. The dynamics in the proteome-map of blood serum in ISH patients revealed the molecular mechanism of neuro-, cadio- and vascular protective effects of amlodipine and valsartan, as a geroprotective mode of drug action.

Competing interests

The authors declare that they have no competing interests.

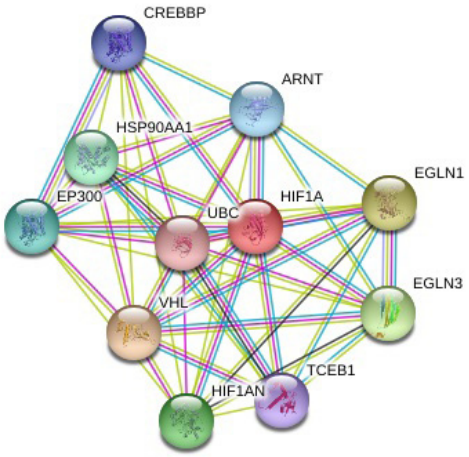

Fig. 1. Molecular interactions of HIF-1alpha (STRING 10.0 database)

VHL-von Hippel-Lindau tumor suppressor, E3 ubiquitin protein ligase; EGLN1-egl nine homolog 1; EGLN3 - egl nine homolog 3 (C. elegans); HIF1AN-hypoxia inducible factor 1, alpha subunit inhibitor; HSP90AA1-heat shock protein 90kDa alpha (cytosolic), class A member 1; EP300-E1A binding protein p300; ARNT-aryl hydrocarbon receptor nuclear translocator; CREBBP-CREB binding protein; TCEB1-transcription elongation factor B (SIII), polypeptide 1; UBC- ubiquitin C.

References

1. Nielsen WB, Vestbo J, Jensen GB. Isolated systolic hypertension as a major risk factor for stroke and myocardial infarction and an unexploited source of cardiovascular prevention: a prospective population-based study. J Hum Hypertens. 1995; 9(3):175-80.
2. Boutouyrie P, Tropeano A, Asmar R, Gautier I, Benetos A, Lacolley P, at al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension. 2002. 39(1):10-5.
3. McEniery CM1, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol. 2005; 46(9):1753-1760.
4. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.