
Comprehensive analysis of the end-organ lesion in hypertensive patients

Mohannd Abdulrazzaq Gati

P.H.D. "physiology of human and animals"

University of Thi-Qar

College of Science

Department of Biology

Hospital of Al-Hussein

Heart center in Nasiriyah

Department of Heart disease

E-mail: mohanndabdulrazzaqgati@yahoo.com

Keywords: arterial hypertension, end-organ lesion, heart failure, microcirculatory disorders

Background. Arterial hypertension (AH) is a serious public health problem in most developed countries. It takes more and more attention of researchers and doctors all over the world [5, 21]. However, the role of the microcirculation disorders and endothelial dysfunction in the pathogenesis of heart failure is still not fully clear. Endothelium regulates not only the peripheral blood flow, but also other important functions, and the state of tissue perfusion determines the functional reserve of the target organs in hypertensive patients [11, 16, 24].

Until 2003 the eye also considered a target organ in hypertension due to the specificity of changes in the retina, which had prognostic value [4, 30, 36]. However, in 2003 European Society of Cardiology (ESC) excluded eye from the list of target organs [7, B32]. At the same time, recent studies prove the existence of a close connection of retinal vascular disorders with target organ lesions in hypertensive patients, the risk of CHD, stroke [3, 13, 18]. Therefore, it is important to study the functional symptoms of hypertensive retinopathy [1, 9, 29].

Therefore a comprehensive assessment of the target organs in hypertensive patients is required to determine the severity of hypertension and the risk of cardiovascular complications, which is valuable in prognosis [27, 35].

Study Objective. This study was designed to determine the end-organ condition under the progression of hypertension and to identify additional criteria of target organ lesion.

Materials and methods

This study presents the results of clinical and instrumental examination of 102 patients with hypertension (Table No. 1).

Depending on the level of casual blood pressure all the subjects were divided into 3 groups according to the degree of increase in blood pressure (BP), according to the European guidelines. Group 1 consisted of the patients with systolic 140-159 mm. Hg and diastolic blood pressure 90-99 mm Hg. Group 2 consisted of the patients with systolic 160-179 mm. Hg and diastolic blood pressure 100-109 mm Hg. Group 3 consisted of the patients with systolic BP >180 mm. Hg and diastolic blood pressure >110 mm Hg.

There was no significant difference in sex and age between groups.

Table No.1

Characteristics of examined patients

evidence	Group 1 (n = 34)	Group 2 (n = 38)	Group 3 (n = 30)
Age, years	49.3 ± 2.6	54.4 ± 4.3	56.8 ± 3.3
Men / Women	9/25	7/31	8/22
The duration of hypertension, years	14.5 ± 1.6	18.4 ± 1.3	20.2 ± 1.8
Quetelet index, kg / m²	26.86 ± 0.9	30,3 ± 1.2	30.9 ± 0.9
Heart rate in beats per minute	68.5 ± 1.9	71,3 ± 1.2	70.6 ± 1.7
Casual SBP, mm Hg	145.1 ± 2.7	167.3 ± 3.2	189.1 ± 2.6
Casual DBP, mm Hg	94.2 ± 2.4	106.7 ± 1.6	114.3 ± 1.8
Family background (%) *	94.6	66.7	51.4

Note: * - number of patients with a cardiovascular

disease in relatives

We excluded patients with heart failure, angina, high functional classes of HF, various arrhythmias and heart defects, diabetes mellitus and other endocrine diseases, symptomatic AH and other conditions which could affect the results of the study [19].

In addition, patients older than 60 were not included in this study because this age group develops more generalized or focal narrowing of the retinal vessels, which does not allow to interpret changes in the retina.

All subjects signed informed consent to participate in the study.

Patients who met the screening criteria canceled prior antihypertensive therapy for 2 weeks before inclusion. In order to control blood pressure and prevent possible complications associated with the withdrawal of the drug, all the patients were hospitalized.

Clinical examination was conducted for 5-7 days, and then patients were prescribed antihypertensive therapy with subsequent control of blood pressure.

All patients underwent a comprehensive examination:

1. General methods: clinical and biochemical blood tests (including uric acid, cholesterol, HDL, LDL), urinalysis, blood glucose, oral glucose tolerance test (OGTT) coagulation (APTT, prothrombin index, fibrinogen) 12-lead ECG.

2. Extra Methods: ambulatory blood pressure monitoring (24h BPM) [15], echocardiogram [10].

3. The study of blood and plasma viscosity, platelet-vascular hemostasis.

4. The study of endothelial function markers:

· Nitrates and nitrites blood plasma were determined by spectrophotometry.

5. Investigation of microcirculation by laser Doppler flowmetry was performed using BLF 21 device

(Transonic Systems Inc., US).

6. The study of the visual analyzer functions:

- direct and indirect ophthalmoscopy,
- electroretinography (ERG). We investigated the maximum and macular ERG to red, green and blue stimuli, recorded with the help of electroretinography.

Statistical analysis was performed using statistical software Excel 2015 and Biostat. The nature and closeness of the relationship of various parameters were determined by calculating the Spearman coefficient of rank correlation [26]. In this regard, we consider weak in its value from 0 to ± 0.29 , average - from ± 0.3 up to ± 0.69 , - strong from ± 0.7 up to ± 1 . If the correlation coefficient p exceeded mistake not less than 3 times, it was considered significant.

RESULTS AND DISCUSSION

Analysis of metabolic risk factors

We have analyzed the following metabolic risk factors:

1. The level of fasting blood glucose (was measured in patients with the level of this parameter above 5.6 mmol/L, or in the presence of one or more risk factors). Patients with dysglycemia were identified: impaired fasting glucose and impaired glucose tolerance.
2. Obesity was diagnosed, when body mass index was above 30 kg/m².
3. Dislipidemiya was evaluated following the Recommendations of European Society of Cardiology/European Society of Atherosclerosis, 2012. The significant value was obtained only for increased level of cholesterol in Group 3.

The analysis of metabolic risk factors (RF) in percentage in different groups revealed a clear pattern: with the increase of disease severity there was an increase in the number of patients with metabolic risk factors and increase in the percentage of patients with a combined two or three RF, which certainly indicates a high risk of cardiovascular e in individuals in group 3. Among the combined RF dyslipidemia and obesity, and dysglycemia and obesity were most common.

Patients were measured their uric acid, considered as one of additional risk factors. No significant changes in this parameter were found, but Group 3 showed a tendency to improve it.

45 (44.2%) patients had such risk factors as hypodynamia and smoking history about 15.3 ± 4.2 years. Interestingly, all patients with dyslipidemia or obesity were included into this group.

Status of the central and peripheral hemodynamics

Characteristic of BP daily profile (24h BPM)

Analysis of circadian blood pressure profile showed that with an increase in the severity of hypertension there was an increase of pathological types of "non - dippers" and "night - pickers", such as a decrease in the physiological "dippers".

Accordingly, with the increase in the hypertension degree there was a statistically significant increase in the average daily figures of systolic blood pressure and diastolic blood pressure, the degree of hypertension

load, the magnitude and speed of morning rise in blood pressure, blood pressure variability, especially at night.

Distribution of hypotensive patients based on the degree of blood pressure elevation was carried out taking into account the measurements of office blood pressure as per the classification ESH/ ESC 2015. Our results of 24h BPM measurements confirmed the correctness of group distribution of patients and, therefore, the adequacy of office blood pressure values.

Characteristic morphological and functional cardiac parameters

The morphological and functional myocardial disorders were found to deteriorate with the disease progression, as a number of patients with left ventricular (LV) remodeling increased. In Group 1 LV hypertrophy was not been identified yet, but there was a concentric remodeling as the initial sign of the morpho-functional LV changes in hypertension. Patients in Group 2 and Group 3 were found to have more severe types of LV remodeling in the form of concentric and eccentric hypertrophy LV, which was associated with an increase in the pressure load on the myocardium.

All groups had an increase in left ventricular posterior wall thickness in diastole: by 20.2% ($p < 0.05$), 23.6% ($p < 0.01$), 27.0% ($p < 0.01$) in Group 1, Group 2, and Group 3, respectively. Change in the interventricular septum thickness in Group 1 patients was not significant, in patients of Group 2 and Group 3 it increased by 11.7% ($p < 0.01$) and 18.9% ($p < 0.01$), respectively. No significant changes of LV myocardial mass was found, but the LV myocardial mass index was increased in Group 2 and Group 3 patients by 15.8% ($P < 0.05$) and 10.6% ($P < 0.05$), respectively.

Diastolic dysfunction of the left ventricle, which is known to be the earliest heart disease symptom, was found in all groups: in Group 1 patients it was insignificant, but with an increase in the severity of hypertension its degree increased. Significant changes were found only in group Group 3 in the form of increased E/A and IVRT by 16.3% ($p < 0.05$) and 36.4% ($p < 0.05$), respectively.

Status of blood rheology, coagulation and platelet aggregation

No significant changes were found in coagulation parameters compared to normal values, only Group 3 showed a tendency toward an increase in the level of plasma fibrinogen.

Group 1 had no significant changes in blood viscosity parameters, but there was a decrease in the index of red blood cells deformation by % 13.6 ($p < 0.05$). Group 2 and Group 3 showed an increase in blood viscosity at V200 by 14.7 ($p < 0.05$) and 11.8 ($p < 0.05$), and a decrease in EDI by 11.8 ($p < 0.05$), and 20.0 ($p < 0.01$), respectively.

In group 1 minor changes in platelet-vascular hemostasis were identified in the form of increased spontaneous platelet aggregation by 26.7 ($p < 0.05$). Group 2 and Group 3 patients showed an increase in the relative aggregate radius with spontaneous aggregation at minute 2 by 32.5% ($p < 0.01$)% and 36.7% ($p < 0.01$), with 0.5- μ M ADP -induced aggregation of wave 1 - by 22.3% ($p < 0.05$) and 24.4% ($p < 0.05$), and with 5.0- μ M ADP - induced aggregation - by 25.8% ($p < 0.05$) and 27.4% ($p < 0.05$), respectively.

Thus, with the increased hypertension degree there was a significant increase in blood viscosity and increase in platelet aggregation, which in its turn exacerbated the changes in microvasculature and endothelial dysfunction.

Assessment of endothelial function

Our results demonstrated the presence of endothelial dysfunction in our patients, which increased with

greater disease severity (Table. No.3).

Table No.3

Endothelial function parameters in three groups with different degree of BP elevation

<i>Nitrites and nitrates, μm</i>			$\Delta\%$
<i>norm 9.76 ± 0.01</i>	Group 1	$12.0 \pm 0.03^*$	+ 23.0% *
	Group 2	$4.13 \pm 0.02^*$	-57.7% *
	Group 3	$4.86 \pm 0.03^*$	-50.2% *

Note: p - significant differences in parameters compared to the norm:

* - $P < 0.05$, ** - $p < 0.01$ (Data are shown as $M \pm m$)

Even Group 1 patients had a significant increase in the level of nitrates and nitrites by 23.0% ($p < 0.05$). This is due to the increased production of cytokines by macrophages, which is caused by a genetic immune system dysfunction, or by other factors, e.g., by high blood pressure. Cytokines induce synthesis of inducible NO synthase (iNOS). iNOS induction at early hypertension stages has a compensatory value, because it limits the rise of blood pressure. This suggests an early impairment of endothelium as a target organ, when blood pressure is either increased insignificantly, or its elevation is not revealed.

With an increasing of hypertension degree, we observed the opposite situation: a significant decrease in the level of these indicators in Group 2 by 57.7% ($p < 0.05$) and Group 3 by 50.2% ($p < 0.05$). This may be explained by the fact that the excess of NO inhibits the activity of endothelial NO synthase (eNOS) and induces vascular cell damage, therefore, there is progressive decline in endothelial NO production and endothelium-dependent vascular relaxation.

Evaluation of the retinal functional status

Ophthalmoscopic picture was presented by vascular (arteriolar narrowing, abnormal arteriovenous chiasms of various degrees, unevenness of arterial and venous caliber) and extravascular changes (hemorrhage, ischemic lesions, solid exudates) (Table No.4).

Table No. 4

Ophthalmoscopic profile in patients with hypertensive retinopathy (number of eyes)

Diagnosis	Vascular disorders	Extravascular disorders	Total
Group 1	45	3	48
Group 2	46	24	70
Group 3	16	28	44

The percentage of patients with more severe extravascular impairments increased with higher hypertension degree.

Bioelectric activity of the retina (electroretinography)

ERG is a graphical representation of bioelectrical activity of the retina that occurs in response to light

stimulation.

In our work, we studied the retina bioelectric activity disorders on the example of the maximum and chromatic macular ERG.

Maximum ERG is a mixed response, and includes components of cone and rod-retinal systems.

In Group 1 most patients (90.5% of the eyes) had normal amplitude and latency of maximum ERG a - and b -waves. In rare cases, there was prolongation of b -wave latency.

In Group 2 patients had maximum ERG profile differed from normal to super and subnormal values. In the study group in 37.8% of cases, there was a significant, compared with the norm, extension of b-wave latency within the range from 70 to 86 ms (at a rate of 58.7 - 64.2 ms).

In Group 3 patients the profile of the maximum ERG differed from normal to super and subnormal values that led to the dispersion of b -wave amplitude from 205 to 345 microvolts (at a rate of 250 - 355 microvolts) . Changes have occurred in 47.4% of patients. Prolongation of b -wave latency was significant ($p < 0.05$) (Table. No.5) .

Table No.5

Maximum ERG	Group1 (n = 42)			Group 2 (n = 56)			AG3 (n = 36)		
	N	-		N	-		N	-	
The amplitude "a"	38	2	2	41	11	4	20	4	12
Latency "a"	40	-	2	42	-	14	27	-	9
The amplitude of "b"	36	2	4	33	15	8	12	14	10
Latency "b"	35	-	7	35	-	21	20	-	16

Normal (N), subnormal (-) and supernormal () ERG distribution by the number of eyes in each group.

Thus, with higher hypertension degree there was a reduction of eye number with a normal type of ERG and normal latency, and therefore there was a prolonged latency of pathological types.

Chromatic macular ERG allows selecting the functional macular area.

Group 1 patients macular ERG to red stimulus was subnormal, but pathological changes to green stimulus were observed. Macular ERG with blue stimulus characterized a decrease the m amplitude of a - and b - waves, and an increase in m latency. Increased latency ranging from 69.0 to 79.2 msec occurred in almost half of the subjects (at a rate of 65.5 - 70.9 ms).

In group 2 macular ERG to red stimulus was subnormal. A significant decrease was observed in a- and b - wave amplitude in the group 2, compared to group 1 ($p = 0.00$). Changed b -wave latency was also observed. Macular ERG for green stimulus had more of the second variation of indicators: observed a decrease in the amplitude of the a- and b -wave, and its increase. ERG blue stimulus had supernormal or subnormal character. In 50 % of the patients showed a significant, compared with the control group lengthening latency b -wave $p < 0.05$) .

In patients with Group 3 subnormal character of macular ERG to red stimulus is registered in 50% of the

results; amplitude a- and b -waves were significantly lower than in the control group and patients with Group 1 ($p = 0.005$), but was not different from the Group 2. ERG green stimulus was subnormal in most cases. Among the values of the amplitude of the b -wave ERG on macular blue stimulus determined considerable variation from 48.1 to 96.8 microvolts (at a rate of 60.2 - 84.7 microvolts), with a significant difference from the norm ($p < 0.05$). Lengthening latency b -wave was observed in 50 % of patients ($p < 0.05$).

The above-described changes in macular ERG changes are similar to those obtained in the study of the maximum ERG: patients with an increase in the severity of hypertension revealed pathological types of ERG and there was an increase latency b -waves as a consequence of ischemia of the retina, which correlates with pronounced changes in the fundus.

It is necessary to test the functional and structural disorders of the target organs in clinical practice, in particular the visual organ, because early detection of these disorders can prevent or delay the complications of hypertension. Consequently, the data of topography and color contrast sensitivity, ERG in our patients can be regarded as a diagnostic criterion for hypertensive retinopathy, eye disease reflects a target organ in hypertension.

Correlation between morphological and functional characteristics of the cardiovascular system and indicators of microcirculation in patients with varying degrees of hypertension

An analysis of the relationship of central and peripheral hemodynamics, blood viscosity, platelet aggregation and microcirculation in patients with varying degrees of increase in blood pressure was performed by determining the Spearman's rank correlation coefficient.

Correlation relationship between circadian blood pressure profile and microcirculation

In the process of disease progression it was observed an increased number of close links between SBP, DBP and the microcirculation parameters.

The most interesting relationship was detected analyzing the blood pressure variability, with fewer relationship found during the day than at night. In the night close correlation between two values was also found, especially DBP (Table. No.6). It confirms the greater contribution of high diastolic blood pressure during the night hours in the process of remodeling of the microvasculature.

This is important, because of an active mechanism of modulation is determined by the myogenic activity of smooth muscle cells of precapillaries and neurogenic activity, that characterizes the vascular tone.

Thus, analyzing the relationships between central and peripheral hemodynamics, we received following important results. With the higher degree of blood pressure, there was an increase of correlations between the studied parameters. As the hypertension got severe, it was found greater correlation with the variability of blood pressure and active (myogenic and neurogenic activity) and passive mechanisms regulation of microcirculation. than with profiles of SBP and DBP. Therefore, there is a great contribution of the central regulatory systems to the maintenance of microvascular blood flow.

Table No.6

Correlation analysis of central and peripheral hemodynamics parameters, blood viscosity, platelet aggregation and microcirculation in patients with varying degrees of blood pressure was performed by determining the Spearman's rank correlation coefficient.

--

Index	PM (Perf.ed.)			Myogenic activity AIF / LVT 3% X 100 (%)			Heart rate fluctuations ACF / 3% RMS x 100 (%)			Respiratory rate fluctuations ANF / 3% RMS x 100 (%)			Intra-vascular resistance ACF / PM 100% x (%)			IEM (%)			Neurogenic activity of 6 / AIF (%)		
	G1 (N = 34)	G2 (N = 38)	G3 (N = 30)	G1 (N = 34)	G2 (N = 38)	G3 (N = 30)	G1 (N = 34)	G2 (N = 38)	G3 (N = 30)	G1 (N = 34)	G2 (N = 38)	G3 (N = 30)	G1 (N = 34)	G2 (N = 38)	G3 (N = 30)	G1 (N = 34)	G2 (N = 38)	G3 (N = 30)	G1 (N = 34)	G2 (N = 38)	G3 (N = 30)
SAD24, mmHg.				-0.451 **		0.368 *			.469 **	.465 **	.422 **	.396 *									
DAD24, mmHg.					.427 **	.476 **												-0.411 *		-0.345 *	-0.369 **
PAD24, mmHg.							.348 *	.431 **	.372 *				.523 ***	.499 **	-0.554 ***	.544 ***	0.511p<0.005			.365 *	
DAD night mmHg.							.452 p<0.005	.482 **		.445 **	.391 *							-0.354 *	-0.447 **	-0.385 *	
SBP variability night mmHg	-0.345 *				.354 *	.408 *			.469 **												
DBP variability night mmHg		-0.416 **	-0.492 **		.427 **	.387 *	.368 *	.527 ***	.49 **			.363 *							-0.436 **	-0.381 **	
IVRT , ms		-0.454 p<0.005	-0.479 **				.406 *	.531 ***	.42 **				.424 **	.391 *	0.398 *	.447 **	-0.399 *				
E / A	-0.453 **		-0.496 **							.359 *	-0.373 *					.335 *					
cardiac index, l / min / m ²										-0.331 *	-0.414 *				0.39 *	.325 *	.368 *				
LVM index g / m ²				.359 *	.329 *	.476 **		.437 **	.374 *						.377 *				0.35 *		
AP diast thickness					.438 **	.501 **	.468 **	.418 **	.486 **		.361 *	.364 *									
EDI		-0.448 **	-0.497 **										-0.441 **	-0.378 *	+0.346 *	.322 *					
spontaneous aggregation, R, pu.	.447 **	.544 ***	.605 ***										.557 ***	.548 ***	.492 **		-0.389 *				
0.5 induced aggregation, R, pu.	.352 *	.378 P = 0.02	.502 **					-0.338 *	-0.366 *							-0.442 **	-0.541 ***	-0.484 **			
5.0 induced aggregation, %		.418 **	.497 **										.342 *	.542 ***	.489 **						

Note: * - p <0.05, ** - p <0.01, *** - p <0.001 (only reliable results are presented in Table)

Correlation analysis of blood pressure profile and microcirculation

As the hypertension got severe, there was a tendency towards the number and strength correlations between these parameters (Table №6).

There was correlations between the parameters of isovolumetric relaxation of the left ventricle time (IVRT) and the E / A ratio of mitral flow peak, characterizing diastolic LV function, and results of respiratory pulse fluctuations of blood flow, providing passive modulation of blood flow (Tab. No.6).

Consequently, the reflected left ventricular diastolic function parameters primarily interacted with passive mechanisms that regulated blood flow. It can be concluded that the appearance of LV diastolic dysfunction is a predictor of hyperemic changes in the microvasculature.

Correlation analysis of left ventricle geometry parameters and microcirculation

There was an increase in a number of detected correlation relationships between the above parameters and microcirculation measurements, as the hypertension got severe.

Correlation analysis of the left ventricle parameters mostly with active modulation of blood flow (indicators of neurogenic and myogenic activity) showed the relationship between left ventricular remodeling and microvasculature remodeling, which further leads to structural organ changes (Tab. No.6).

These findings indicate a high sensitivity and specificity of the method in studying the microcirculation system.

Correlation analysis of parameters of blood viscosity and platelet aggregation and microcirculation

As the hypertension got severe, the number and strength of correlations with indicators of platelet-vascular hemostasis, blood rheology and microcirculation parameters was increased (Tab. No.6).

Therefore, the higher the degree of BP elevation was, the greater and closer the correlation relations were, that suggests the progression of organ damage with disease aggravation. This demonstrates that the impairment of tissue perfusion is a critical aspect for the development and further damage of target organs in hypertension, independently of what organs they are, and microvasculature itself may be considered as a target organ in hypertension.

CONCLUSIONS

1. With increasing severity of the disease occurs declining of morphological and functional changes in the myocardium, and degree of impairment of left ventricular relaxation. Concentric and eccentric left ventricular hypertrophy developed in Group 1 and Group 2, and the increase in percentage between these two types was observed in Group 3 patients, which proves the primary effect of high blood pressure on target organs. Minimal myocardial changes in Group 1 patients suggests that the earliest possible diagnosis is needed to correct the target organ lesions associated with hypertension.

2. There was significant decrease in NO levels as hypertension got more severe, suggesting the progression of the degree of endothelial dysfunction. For this reason the level of plasma nitrates and nitrites has a great diagnostic and prognostic significance, and vascular endothelium has been identified as a separate target organ.

3. The electroretinography revealed the increase in b-wave latency of maximum and macular ERG with the increased degree of hypertension severity, which is also a measure of the retinal functional state. The above figures may serve as diagnostic and prognostic criteria for hypertensive retinopathy. The results prove that it is early to exclude primary retinal changes from the list of target organs in hypertension.

4. With the disease progression the rate of patients with different metabolic risk factors increases, which also proves that there is high risk of cardiovascular events in patients with severe hypertension.

5. There were correlations found between microcirculation parameters and indicators of central and peripheral hemodynamics, blood viscosity and platelet aggregation. With the increase in the degree of

hypertension, the relationships found got greater in number and closer that demonstrates that organ lesions got more severe with the disease progression. This suggests that microvasculature is an independent target organ in hypertension.

8. The level of tissue perfusion requires comprehensive assessment, it is characterized by the microcirculation status, platelet-and-vascular hemostasis, and endothelial function, which has a great diagnostic and prognostic value in hypertensive patients and affects further disease progression.

LITERATURE

1. Sygit, M., [Complications of arterial hypertension]. *Wiad Lek*, 1983. 36(2): p. 89-93.
2. Ault, M.J. and A.G. Ellrodt, Pathophysiological events leading to the end-organ effects of acute hypertension. *Am J Emerg Med*, 1985. 3(6 Suppl): p. 10-5.
3. Shkhvatsabaia, I.K., A.P. Iurenev, and O.A. Kozdoba, [Lesions of target organs in arterial hypertension]. *Kardiologiya*, 1986. 26(10): p. 75-80.
4. Stanic, R. and I. Lelea, [Problems in arterial hypertension and its most frequent complications--a 10-year statistical analysis of the central Banat region]. *Med Pregl*, 1986. 39(11-12): p. 547-52.
5. Eliahou, H.E. and B. Hellberg, [Arterial hypertension in the diabetic: support of most of its complications]. *Journ Annu Diabetol Hotel Dieu*, 1988: p. 97-104.
6. McCoy, G.C., et al., End organ changes associated with the self-regulatory treatment of mild essential hypertension? *Biofeedback Self Regul*, 1988. 13(1): p. 39-46.
7. da Costa, J.N., [Organ and system involvement in arterial hypertension and its classification]. *Rev Port Cardiol*, 1989. 8(10): p. 671-4.
8. Schachinger, H. and R.E. Schmieder, [Importance of 24-hour blood pressure monitoring in detection of hypertension-induced end organ damage]. *Z Kardiol*, 1991. 80 Suppl 1: p. 41-7.
9. ACE inhibitors and end-organ damage in cardiovascular disease: kidney and nervous system in hypertension. *Proceedings of the Erasmus Medical Workshops. J Cardiovasc Pharmacol*, 1992. 19 Suppl 6: p. S1-145.
10. Grossman, E. and F.H. Messerli, End-organ disease in hypertension: what have we learned? *J Cardiovasc Pharmacol*, 1992. 20 Suppl 10: p. S1-6.
11. Houston, M.C., New insights and approaches to reduce end-organ damage in the treatment of hypertension: subsets of hypertension approach. *Am Heart J*, 1992. 123(5): p. 1337-67.
12. Travaglino, F., et al., [Arterial hypertension and macroangiopathic complications in a group of diabetic out-patients]. *Minerva Med*, 1992. 83(12 Suppl 1): p. 15-8.
13. Fournier, A.M., L.J. Hoenig, and J.M. Sosenko, The degree of blood pressure evaluation and end organ damage with severe hypertension: a case-control study. *Am J Med Sci*, 1993. 306(6): p. 367-70.
14. Licata, G., [Epidemiology of arterial hypertension and organ damage]. *Ann Ital Med Int*, 1994. 9 Suppl: p. 44S-49S.
15. Mancina, G., et al., Blood pressure reduction and end-organ damage in hypertension. *J Hypertens Suppl*, 1994. 12(8): p. S35-41; discussion S41-2.
16. Perloff, D., Retrospective and prospective research on hypertension-related end-organ damage. *J Cardiovasc Pharmacol*, 1994. 24 Suppl A: p. S1-5.
17. Agabiti-Rosei, E. and M.L. Muesan, [The organ damage in arterial hypertension]. *Ann Ital Med Int*, 1995. 10 Suppl: p. 99S-107S.
18. Fagher, B., S. Valind, and T. Thulin, End-organ damage in treated severe hypertension: close relation to nocturnal blood pressure. *J Hum Hypertens*, 1995. 9(8): p. 605-10.

-
19. Schmieder, R.E., et al., Comparison of early target organ damage between blacks and whites with mild systemic arterial hypertension. *Am J Cardiol*, 1997. 79(12): p. 1695-8.
 20. Bataineh, A. and L. Raij, Angiotensin II, nitric oxide, and end-organ damage in hypertension. *Kidney Int Suppl*, 1998. 68: p. S14-9.
 21. Heesen, W.F., et al., Effect of quinapril and triamterene/hydrochlorothiazide on cardiac and vascular end-organ damage in isolated systolic hypertension. *J Cardiovasc Pharmacol*, 1998. 31(2): p. 187-94.
 22. Mule, G., et al., Value of home blood pressures as predictor of target organ damage in mild arterial hypertension. *J Cardiovasc Risk*, 2002. 9(2): p. 123.
 23. Salamatina, L.V., et al., [Organ lesions and chronobiologic structure of circadian rhythm in arterial blood pressure in persons with arterial hypertension]. *Med Tr Prom Ekol*, 2003(4): p. 7-10.
 24. Sica, D.A., Hypertension and end-organ disease in African Americans: case presentations. *J Clin Hypertens (Greenwich)*, 2004. 6(4 Suppl 1): p. 48-53.
 25. Boitsov, S.A., et al., [Structure of risk factors, damages of target organs, and metabolic changes in patients with arterial hypertension of various age groups]. *Kardiologiia*, 2009. 49(4): p. 19-24.
 26. Gapon, L.I., N.P. Shurkevich, and A.S. Vetoshkin, [Structural and functional changes in the heart and 24-hour arterial pressure profile in patients with arterial hypertension in the Far North]. *Klin Med (Mosk)*, 2009. 87(9): p. 23-9.
 27. Li, Y., et al., [Perindopril, amlodipine and telmisartan improve arterial stiffness in patients with hypertension]. *Zhonghua Xin Xue Guan Bing Za Zhi*, 2009. 37(10): p. 908-12.
 28. Irigoyen, M.C., et al., Hypertension, Blood Pressure Variability, and Target Organ Lesion. *Curr Hypertens Rep*, 2016. 18(4): p. 31.
 29. Osborn, J.W., et al., Effect of subfornical organ lesion on the development of mineralocorticoid-salt hypertension. *Brain Res*, 2006. 1109(1): p. 74-82.
 30. Mensah, G.A., Hypertension and Target Organ Damage: Don't Believe Everything You Think! *Ethn Dis*, 2016. 26(3): p. 275-8.
 31. Lackland, D.T., Controlling Hypertension to Prevent Target Organ Damage: Perspectives from the World Hypertension League President. *Ethn Dis*, 2016. 26(3): p. 267-70.
 32. Zhu, W., et al., [Correlation between a blood pressure variability-based scoring system and target organ damage in patients with hypertension]. *Nan Fang Yi Ke Da Xue Xue Bao*, 2016. 36(4): p. 567-71.
 33. Veloudi, P., et al., Blood Pressure Variability and Prediction of Target Organ Damage in Patients With Uncomplicated Hypertension. *Am J Hypertens*, 2016.
 34. Milazzo, V., et al., Cardiac Organ Damage and Arterial Stiffness in Autonomic Failure: Comparison With Essential Hypertension. *Hypertension*, 2015. 66(6): p. 1168-75.
 35. Chen, Y., Y.L. Huang, and W.Y. Mai, Prehypertension or masked hypertension-which is responsible for target-organ damage? *Nat Rev Cardiol*, 2015. 12(8): p. 497.
 36. Marwick, T.H. and A.J. Venn, The Strain of Detecting Early Target Organ Damage in Hypertension. *J Am Coll Cardiol*, 2015. 65(25): p. 2688-90.