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CABAC-POGOREVICI IRINA

INTRARENAL HEMODYNAMICS IN ARTERIAL HYPERTENSION AND DYSGLYCEMIA – THE CONNECTING LINK BETWEEN MICROVASCULAR AND MACROVASCULAR DAMAGE

321.03 - CARDIOLOGY

Summary of Ph.D. Thesis in Medical Sciences

CHIȘINĂU 2019

The thesis was designed at the Department of Internal Medicine, Discipline of Cardiology, PI "Nicolae Testemitanu" State University of Medicine and Pharmacy

Scientific advisor:
Revenco Valeriu,
Habilitated Doctor of Medical Sciences, University professor

Members of the guidance group
Grib Livi
Habilitated Doctor of Medical Sciences, Associate professor

Ochișor Viorica
Ph.D, Associate professor

Mihalache Georgeta
Ph.D, Associate professor

Ph.D. thesis defense will take place on 10.09.2019, 2:00 pm, within "Nicolae Testemitanu" State University of Medicine and Pharmacy, Ștefan cel Mare și Sfânt, 165 Bd, office 205, in the meeing of the Commission for the public defense of the PhD thesis, approved by the decision of the Scientific Council of the Consortium from 03.07.2019, (*protocol nr.3)*

Nominal structure of the Commission for public defense of the PhD thesis:

Chair:
Caproș Natalia
Habilitated Doctor of Medical Sciences, Associate professor

Members:

Vataman Eleonora,
Habilitated Doctor of Medical Sciences, University professor

Revenco Valeriu,
Habilitated Doctor of Medical Sciences, University professor

Ciobanu Nicolae,
Habilitated Doctor of Medical Sciences, Research professor

Grosu Aurel,
Habilitated Doctor of Medical Sciences, University professor

Cobeț Valeriu,
Habilitated Doctor of Medical Sciences, University professor

Grib Livi,
Habilitated Doctor of Medical Sciences, Associate professor

Author
Cabac-Pogorevici Irina

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CONCEPTUAL RESEARCH BENCHMARKS

The research actuality. Today, we witness a steady increase in obesity prevalence, as well as in different types of dysglycemia and cardiovascular diseases (CVD). The overall incidence of arterial hypertension (HTN) accounted for 1.13 billion in 2015, being over 150 million across Eastern Europe. The overall incidence of HTN in adult population is about 30-45%, with an age-adjusted prevalence of 20% and 24% for men and women, respectively. The high rate of HTN is consistent across the globe, regardless of the income level [1]. Hypertension gets more common with aging, being > 60% in the population over 60 years. [2]. It is estimated that the number of hypertensive individuals will have increased by 15-20% before 2025, reaching to almost 1.5 billion of the global population [3]. According to statistical data provided by the World Health Organization (STEPS study), about 40,4% of the population from the Republic of Moldova are hypertensive.

Identifying the risk factors for outlining and implementing the therapeutic and effective treatment approach is one of the desiderata of the field-related researchers [4,5]. Complex therapeutic management and high treatment costs might affect both the physician intervention and appropriate patient′s follow-up [6,7]. Tracing out the predictive markers may help provide appropriate preventive care, which will substantially contribute to reducing the number of newly diagnosed hypertensive patients that tends to constantly increase [8,9].

Similarly, diabetes mellitus (DM) has widely spread among the population worldwide. The increasing incidence of DM led to approximately 360 million people in 2011, of which more than 95% have type 2 DM [10]. It is estimated that these values will increase to 552 million by 2030, although about half of these patients are assumed not being aware of the disease. Moreover, it is estimated that another 300 million individuals show signs of dysglycemia, including impaired fasting glucose, impaired glucose tolerance, gestational diabetes and euglycemic insulin resistance [11, 12]. Most new cases of Type 2 diabetes are related to the "western" lifestyle, characterized by high- fat diet and a reduced physical activity, resulting in high rates of obesity, insulin resistance, compensatory hyperinsulinemia, and ultimately, β-Cell failure in Type 2 diabetes [13] respectively. HTN is commonly encountered in patients with dysglycemia. Recently, it has been proved that sedentary lifestyle and high-fat diet constantly increase the incidence of Type 2 diabetes among young adults and children. Prophylaxis includes two major aspects, namely weight loss and daily physical activity. Diabetic population are at higher risk of developing CVD. Diabetes - associated HTN significantly increases the risk of morbidity and CV mortality rate [14]. All the risk factors associated with dysglycemia suggests that CVD might occur prematurely and before the development of DM per se, wheras strong correlation between hyperglycemia and microvascular disease (retinopathy, nephropathy, neuropathy) indicates that there in no obvious risk until a hyperglycemia develops. These patterns reveal the progressive feature of both Type 2 diabetes and CVD - associated risk, which poses life-threatening challenges to the diabetic patient. The effects of aging, comorbidities and involvement of specific population groups require identifying the risks in an individualized way in order to allow the patient to play a major role in the disease management [15]. Dysglycemia, defined as impaired fasting glucose, impaired glucose tolerance, increased HbA1c, and diabetes mellitus is characterized by elevated circulating glucose [13, 16].

Type 2 diabetic patients may remain asymptomatic for a long time, showing high levels of serum glycemia, blood pressure and serum cholesterol. Actually, the diagnosis is not confirmed until severe complications develop, thus involving more considerable effort and higher costs.

Therefore, it is crucial to identify patients with dysglycemia on time, as the disease progresses rapidly from uncomplicated type 2 DM to type 2 DM and thus might be slowed down or even stopped by modifying the lifestyle or administrating drugs [17]. Patients are most commonly diagnosed with DM or impaired glucose tolerance when they have already developed subclinical atherosclerosis [18, 19]. Thus, the early detection of dysglycemia and its possible complications in hypertensive patients would fICAlitate the implementation of preventive measures against CV complications [20]. Therefore, it is undoubtedly necessary to develop methods that would identify patients at high risk of developing complications from the early stages of DM, allow applying therapeutic strategies for the most susceptible population, and prevent the development of DM, as well as its onset and progress of complications that have already established [21].

Recent studies pay more attention to intrarenal hemodynamics (IRH) as a marker of HMOD in patients with HTN, the renal resistance index (RRI) being an early potential detector of vascular damage at microvascular and macrovascular level in hypertensive and dysglycemic patients [22, 23].

Therefore, identification of IRH particularities in hypertensive patients is of a particular medical and scientific interest, which depends on different types of dysglycemia, as well as on the interdependence of these parameters with HMOD both within central and peripheral vascular artery beds [4].

Purpose of Study:

The importance of the assessment of intrarenal hemodynamics as a marker of microvascular and macrovascular diseases in arterial hypertension and dysglycemia.

Objectives:

1. Assessment of intrarenal hemodynamics According to clinical, hemodynamic and anthropometric parameters in hypertensive patients.
2. Estimating the correlation between the parameters of carotid and intrarenal hemodynamics with the severity of carotid atherosclerosis in arterial hypertension.
3. Correlation analysis of left ventricular geometry and systolic / diastolic function parameters with indices of intrarenal hemodynamics in hypertensive patients.
4. Study of the nictemeral patterns of systolic and diastolic blood pressure and their interdependence with asymptomatic target organ damage in hypertensive patients.
5. Assessment of intrarenal hemodynamics according to microvascular impairment in patients with hypertension and dysglycemia.
6. Comparative study of intrarenal hemodynamics with microvascular and macrovascular disease indices in cases of hypertension and dysglycemia.

Scientific novelty of the research:

This is a clinical study, that aimed at studying RF, microvascular and macrovascular disease in patients with HTN and dysglycemia, as well as their correlation with IRH parameters. We analyzed the particularities of hemodynamics at different levels of the CV system, determining both interdependence and their correlation with IRH and general atherosclerotic burden. IRH parameters proved to be necessary and useful in the patient assessment algorithm for HTN and dysglycemia.

Theoretical significance:

The results of the study help outline the pathophysiological, clinical and hemodynamic determinants in HTN and dysglycemia, elucidate the authentic identity of the IRH parameters, as well as identify their potential diagnostic and prognostic values in CV disorders. So far, IRH has been considered an echo of intrarenal vascular disease, whereas the study outcomes have proved that IRH changes are associated with a complex interaction of both systemic and renal vascular properties and haemodynamic factors. RRI has been outlined as a measurement unit of intrarenal and systemic vascular resistance, which allowed us to demonstrate its potential relationship with extrarenal hemodynamic factors, thus validating its association with HMOD in hypertensive patients and being a predictor of microvascular and macrovascular dysfunction within various types of HTN- associated dysglycemia.

Application value of the topic:

To identify the importance of IRH in HMOD assessment among HTN and dysglycemia-diseased patients that would suggest a strong correlation between intrarenal vascular resistance and morphological and haemodynamic changes within the CV system. The results of the study might encourage the use of IRH parameters as well as of carotid hemodynamics within the algorithm assessment of patients with HTN and dysglycemia. Ambulatory blood pressure monitoring is recommended for all hypertensive patients, especially in presence of HMOD on macrovascular (carotid arteries, peripheral arteries), microvascular (retinopathy, nephropathy, peripheral neuropathy), and heart levels (left ventricular hypertrophy, left ventricular (LV) diastolic dysfunction, cardiac remodeling). This might become a new useful and non-invasive parameter of vascular damage in HTN and dysglycemia-diseased patients among the multiple variables obtained during our study of IRH and RRI, thus being identified as a potential link between microvascular and macrovascular disease.

Implementation of scientific results:

The study outcomes were implemented within the clinical activity of the Institute of Cardiology, the Municipal Clinical Hospital "Holy Trinity" as well as during the teaching activity at the Department of Cardiology and Department of Internal Medicine of "N. Testemitanu" SUMPh.

1. RESEARCH METHODOLOGY

The current research was focused on a controlled clinical trial. The current study was based on a drafted methodological research plan, involving the selective criteria for the patients included within the study; elaboration and completion of the research forms; analysis, synthesis and interpretation of the obtained results; implementing the study outcomes into practice. The research was conducted during the years 2016-2018 in CCAordance with WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. The study was initiated after signing the informed consent by all the participants (Patient Information and CCAeptance form), which got familiar with the assessment methods that were going to be applied at initiation and during the study. Patient confidential and ethical standards have been followed.

The required number of research units to be included within the study was determined based on the following formula:

$$n = \frac{1}{(1-f)} \times \frac{2(Z_\alpha + Z_\beta)^2 xP(1-P)}{(P_o - P_1)^2}$$

whereas:

Po - the mean distribution of hypertensive patients makes up 39.0 % (P0 =0,39).
P1 – we assume that the value of the study group will be 61.0 % (P1 =0,61).
P =(P0 + P1)/2 =0,50
Zα – table value. For statistically significant results of 95.0 %, the coefficient Zα =1,96
Zβ – table value. For comparison of the statistical power of 80,0 %, the coefficient Zβ =0,84
f =The expected distribution of patients who were likely to abandon the research for any other reasons, regardless of the investigated effect q =1/ (1-f), f=10,0 % (0,1).

The following value has been obtained by inserting the data into the formula:

$$n = \frac{1}{(1-0{,}1)} \times \frac{2(1.96+0{,}84)^2 x 0{,}50 x 0{,}50}{(0{,}39-0{,}61)^2} = 99$$

The patients were assessed via a specific questionnaire, which included:
1. General physical examination via multiple anthropometric measurements;
2. Laboratory investigations: complete blood count, serum biochemistry (urea, creatinine, glycemia, glycaemic profile, HbA1c, bilirubin level, ionogram, total serum cholesterol, triglycerides, high and low-density lipoproteins), urinalysis, albuminuria, and creatinine urine test;
3. Instrumental investigations: Twelve-lead electrocardiogram at rest, cycle ergometer test , transthorICAc color and pulsatile Doppler echocardiography, ultrasound image of the abdominal cavity organs + adrenal glands, Doppler ultrasound of primary and parenchyma renal arteries, carotid Doppler ultrasonography, retinoscopy, neurological exam, Ambulatory Blood Pressure Monitoring (ABPM), and ambulatory ECG (Holter) monitoring .
4. Coronary angiography, superselective aortaography and angiography of the renal arteries, serum and urine hormone testing (metanephrine, cortisol, aldosterone), and computed abdominal tomography were carried out if required.

Inclusion criteria of the study group

Stage I-III hypertension in patients aged 18 - 79 years, including HTN associated with dysglycemia.

Exclusion criteria of the study group:

• Stable angina pectoris
• Unstable angina pectoris
• Coronary or peripheral revascularization
• Acute myocardial infarction, old myocardial infarction
• Cardiomyopathy
• Heart failure, including heart failure with preserved ejection fraction
• Severe arrhythmias, including atrial fibrillation
• Previous ischemic or acute haemorrhagic cerebrovascular diseases
• Insulin-dependent type 1 and type 2 diabetes mellitus
• End-stage renal disease (STAGE IV + K / DIGO, dialysis)
• Kidney post-transplantion patients
• Acute or chronic obstructive nephropathy and uropathy
• Unilateral or bilateral stenosis of renal arteries of significant hemodynamics
• Myelodysplastic syndromes

• Tumors
• Alcoholism or drug abuse
• Technical limitations of imaging methods

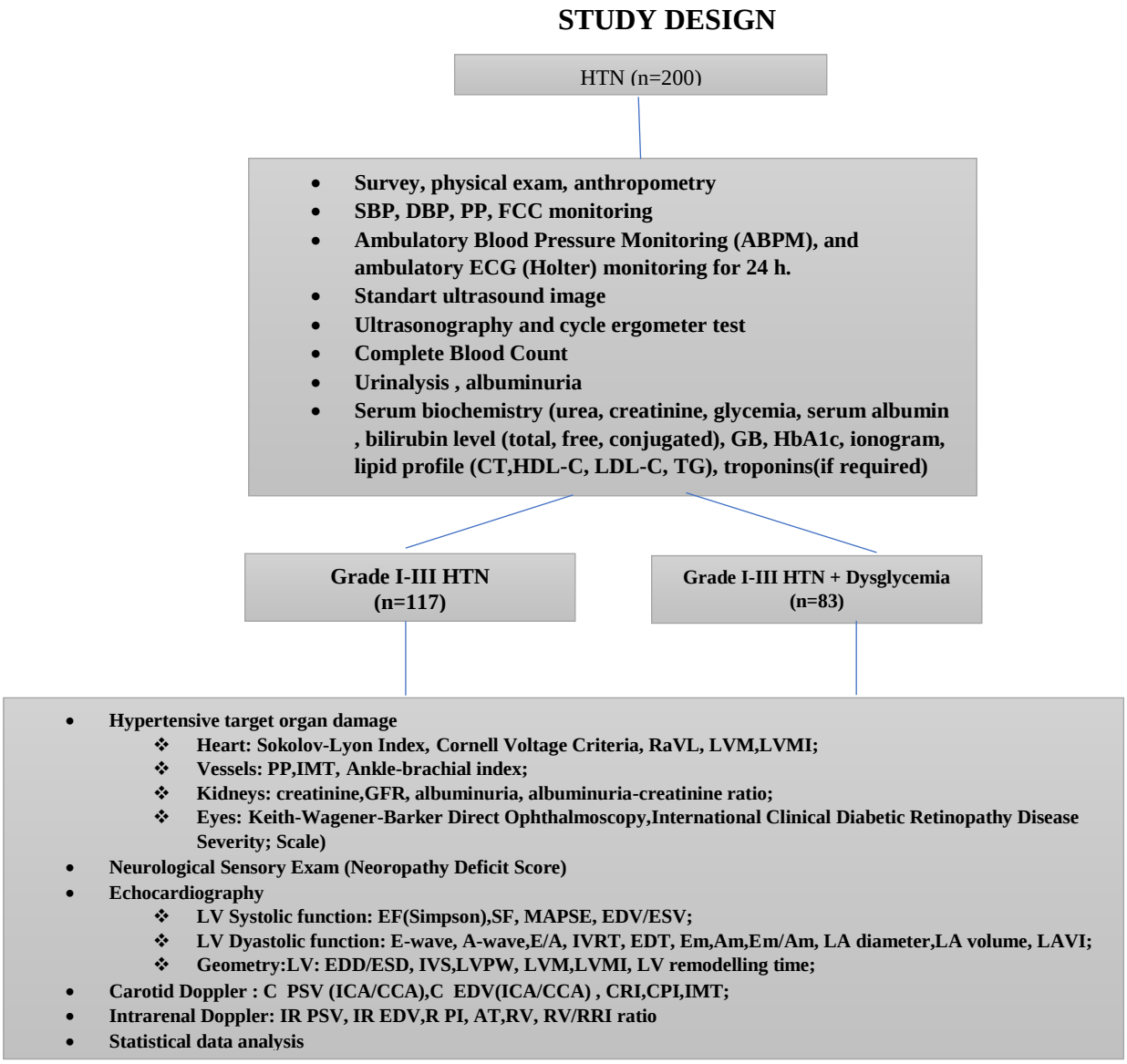

Figure 1. **Study design**

2. STUDY OUTCOMES

2.1 Clinical and hemodynamic characteristics of hypertensive patients

The research included 200 patients with HTN aged 18-79 years, the mean age being of 50,15 ± 14.50 years, whereas 56% (112 patients) of the total studied population were men and 44% (88 patients) were women, respectively. The patients's assessment according to their social status and daily physical activity showed the following data: the prevalence was higher in urban patients - 65% (130 patients) compared to those from rural areas - 35% (70 patients); most patients were engaged employees – 68,5% (137 patients), which was also noted in physical activity assessment, thus 63,5% of the patients showed the lowest physical activity level; patients with sedentary lifestyle - 69%, whereas 64% of cases showed minimal physical activity, 30% - moderate physical activity and only 6,5% - high physical activity. Of all patients included in the study, 22% (45 patients) were reported as smokers with mean duration of smoking of 22,27 ± 11,96 years and the mean smoking pack years of 21,09 ± 4,86.

The analysis of BP values showed that 22% (44 patients) had stage I HTN, 48% (96 patients) - stage II HTN and 30% (30 patiens) – stage III HTN , whereas the mean age of HTN onset was 40,55 ± 10,27 years, the mean HTN duration being of 9,57 ± 7,12 years.

The mean values of hemodynamic indices were found as follows: daytime SBP was 153,73 ± 12,82 mmHg, nighttime SBP – 138,32 ± 16,35 mmHg, mean SBP – 146,12 ± 13,96 mmHg, daytime DBP – 91,32 ± 6,05 mmHg, nighttime DBP – 81,79 ± 8,34 mmHg, mean DBP - 86,59 ± 6,78 mmHg, daytime PP – 63,29 ± 9,57 mmHg, nightime PP – 57,34 ± 11,38, mean PP – 60,34 ± 9,98 mmHg, daytime HR 86,06 ± 8,85 b/min, nighttime HR 62,97 ± 7,91 b/min, mean HR 75,29 ± 7,04 b/min.

The assessment of carbohydrate metabolism changes showed that 52% of the population from the general group had different types of dysglycemia, 17,5% (35 patients) -Type 2 diabetes with an average disease duration of 8,68 ± 3,78 years, 15% (30 patients) - IGT, 19,5% (39 patients) - IFG, and 26,5% (53 patients) with exacerbated family history for diabetes. Microvascular impairment in diabetic patients exhibited the following data: diabetic retinopathy in 16% (32 paitnets), of which 62,5% had grade I diabetic retinopathy, 31,3% - grade II diabetic retinopathy, and 6,3% - grade III retinopathy. Distal symmetric peripheral diabetic neuropathy was found in 16% of patients, of which 75% of cases showed mild, 21,9% - moderate and 3,1% - severe neuropathy. Albuminuria and glucosuria were found in 8% and 5% of patients, respectively, of which 81,3% exhibited light albuminuria.

The mean IRH values within the parenchymal renal arteries were as follows: right kidney mean RRI 0,6672 ± 0,0452, left kidney mean RRI 0,6685 ± 0,0458, right kidney mean IPR 1,246 ± 0,181, left kidney mean IPR 1,2533 ± 0,178, right kidney mean AT 66,68 ± 2,324, left kidney mean AT 66,66 ± 2,488, right RV 129,27 ± 23,785 ml, left RV 129,52 ± 25,078 ml, right kidney mean RV/RI ratio 93,07 ± 40,21 ml, left kidney mean RV/RI ratio 195,52 ± 41,587 ml.

Carotid Doppler assessed haemodynamic parameters revealed right common carotid artery CRI 0,7991 ± 0,042, left common carotid artery CRI 0,8037 ± 0,044, right internal carotid artery CRI 0,7472 ± 0,041, left internal carotid artery CRI -0,7457 ± 0,043, common right carotid artery CPI 1,4127 ± 0,243, left common carotid artery CPI 1,4157 ± 0,248, right internal carotid artery.

Table 1. **Mean values for intrarenal Doppler parametres**

Parametrul	Minimal value	Maximal value	Mean value	Standard deviation
Right kidney mean RRI	0,56	0,82	0,67	0,05
Left kidney mean RRI	0,57	0,84	0,67	0,05
Right kidney mean RPI	0,89	2,32	1,25	0,18
Left kidney mean RRI	0,87	2,32	1,25	0,18
Right kidney mean AT	57,00	71,00	66,68	2,32
Left kidney mean AT	56,60	74,00	66,66	2,49
Right RV	77,00	213,00	129,27	23,79
Left RV	43,00	200,00	129,52	25,08
Right kidney RV/RRI ratio	107,00	338,00	193,07	40,21
Left kidney RV/RRI ratio	112,00	322,00	195,52	41,59

Notă: *RRI – renal resistive index; RPI – renal pulsatility index; AT Acceleration time; RV – renal volume*

2.2 Intrarenal hemodynamic parameters according to clinical and anthropometric hemodynamic variables in hypertensive patients

The univariate analysis showed an age-related positive correlation of RRI, RPI, AT, RV and RV/RRI ratio (r =0,534, p <0,01, r =0,376, p <0,01, r =0,372, p <0,01, r =0,207, p <0,01, r =0,347, p <0,01), which proved to be significant for RRI, moderate for RPI and VR/RRI ratio, and weak for RV. Female RRI, RPI and AT values were higher compared to males, however, not being statistically significant, whereas RV and RV / RRI ratio were higher and statistically significant for males (133,06 ml vs 124,41 ml, p <0,01, 201,43 ml vs 187,88 ml, p <0,01).

Higher values of IRH parameters were found in smokers, but these were not statistically significant (p >0,05). However, a moderate-statistically significant correlation of RRI with the mean smoking pack/years (r =0,352, p <0,05, r =0,315, p <0,05) was recorded.

The study of IRH parameters associated with HTN grading resulted in the following data: increase of renal RRI, RPI and AT is related to increase of HTN grade (RRI =0,634, PI =1,239, AT =65,673 ms for grade I HTN; RRI =0,666, RPI =1,247, AT =66,703 ms for grade II HTN; RRI =0,694, RPI =1,343, AT =67,368 for grade III HTN, p < 0,05), whereas the decrease of RV values and RV/RRI ratio depends on increase of HTN grade (Figure 2).

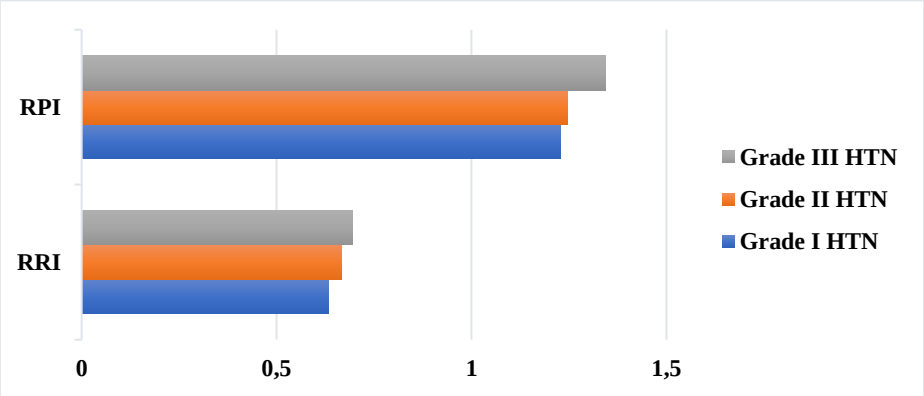

Figure 2. IRH parameters changes depending on HTN grade

Note. p <0,05 – differences between the IRR, IPR values according to the HTN grade

The comparative analysis of IRH variables with systematic antihypertensive treatment has reported higher, statistically significant values for RRI (0,648 vs 0,680, p <0,001), and for RPI (1,204 vs. 1,286, p < 0,01) in patients undergoing systematic antihypertensive therapy. However,

there were higher RV values (134,97 vs 125,14 p, <0,01) and RV/RRI ratio (207,40 vs 183,26, p <0,01) in patients who did not receive antihypertensive treatment (Figure 3).

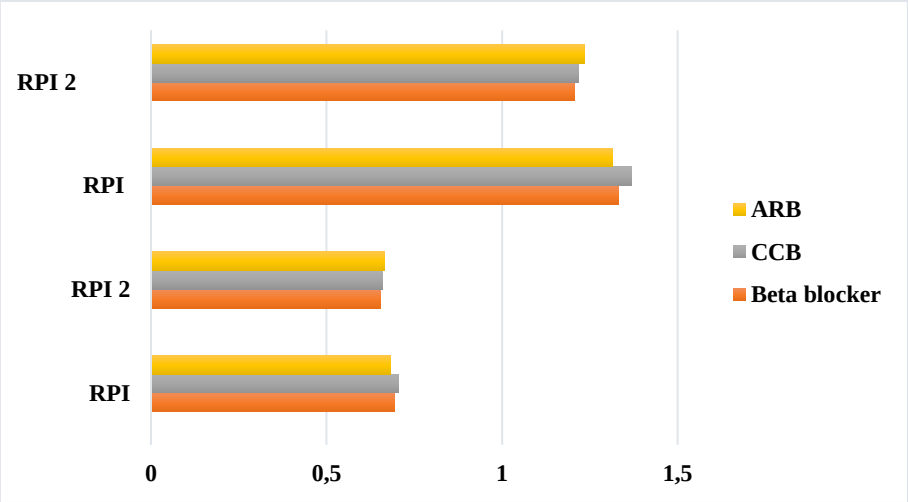

Figure 3. Variations of IRH parameters depending on the type of antihypertensive therapy

Notă. Differences betweem IRR, IPR according to the type of antihypertensive treatment, p <0,05 – angiotensine receptors blockers, p <0,01 – calcium chanel blockers, p <0,001 – betablockers.

In the comparative analysis of IRH values with retinal damage in HTN, the following findings were made (Figure 4): patients with hypertensive retinopathy exhibited higher RRI values (0,651 vs 0,685, p <0,001), RPI (1,19 vs 1,31 p <0,001), AT (66,22 vs 67,18, p <0,01) versus those without retinopathy, and lower RV values (132,81 vs 125,42 p <0,05) and the RV/RRI ratio (203,28 vs 181,87, p <0,001). The values of some IRH parameters increased with grade retinopathy (Grade I vs. Grade II vs Grade III), RRI (0,669 vs 0,699 vs 0,734, p <0,001), RPI (1,271 vs 1,317 vs 1,546, p <0,001), other parameters such as AT were indifferent while RV (130,20 vs 121,77 vs 109,32, p <0,05) and the RV/RRI ratio (191,37 vs 174,93 vs 148,78, p <0,01) decreased as the rate of hypertensive retinopathy increased.

The comparison of the degree of peripheral vascular damage determined by ABI with IRH variables, showed maximal RRI values (0,706 vs 0,675 vs 0,655, p <0,001), RPI (1,346 vs 1,267 vs 1,214, p <0,001) in patients with peripheral arterial disease compared to those with baseline and normal values, no statistically significant variations were observed for the presence of peripheral arterial disease, and for the RV/RRI ratio (ABI - 172,36 vs baseline values – 192,01 vs normal – 202,28, p <0,01), there is a decrease in its values with the progression of peripheral vascular damage.

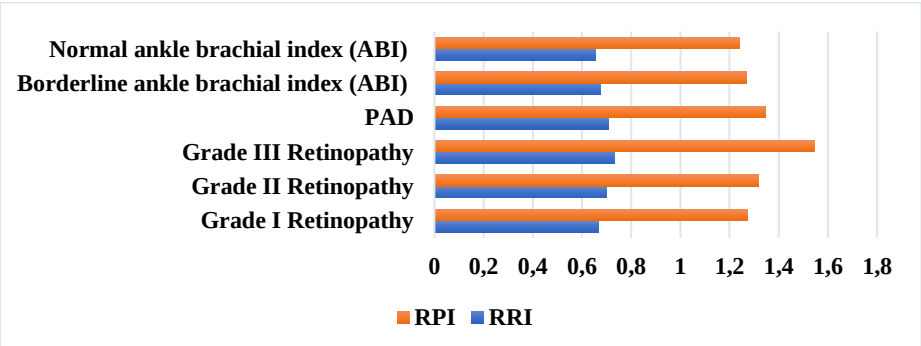

Figure. 4. Correlation of IRH parameters with HTN-related vascular damage

Note. p <0,001 - differences in RRI and RPI values depending on the degree of retinopathy and the presence and degree of peripheral artery disease.

The study recorded statistically significant correlations of systemic haemodynamic parameters with IRH parameters, particularly for RRI and hemodynamic parameters, namely daytime SBP (r =0,319, p <0,01), nighttime SBP (r =0,252, p <0,01), mean SBP (r =0,302, p <0,01), daytime DBP (r =0,264, p <0,01), nighttime DBP (r =0,228, p <0,01), mean DBP (r =0,225, p <0,01), daytime PP (r =0,286, p <0,01), nighttime PP (0,222, p <0,01), mean PP (r =0,277, p <0,01) daytime HR (r =-0,170, p <0,01), nighttime HR (r =-0,148, p <0,01), mean HR (r =-0,166, p <0,01) (Figure 5).

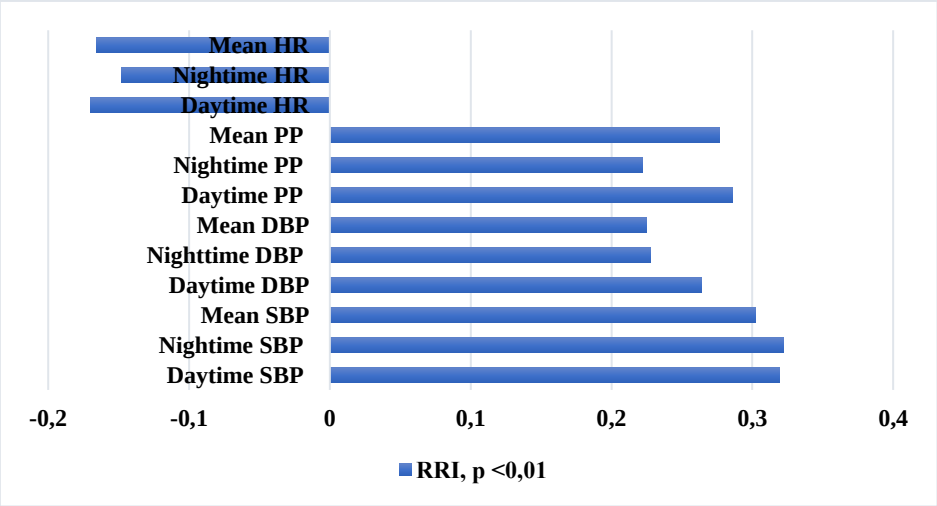

Figure 5. RRI correlation with systemic haemodynamic parameters

Note. p <0,01 - RRI correlations with daytime HR, nighttime HR, mean HR, daytime PP, nighttime PP, mean PP, daytime SBP, daytime SBP, mean SBP, daytime DBP, nighttime DBP, mean DBP.

2.3 Left ventricle geometry, systolic and diastolic function parameters and intrarenal hemodynamics in patients with HTN.

A correlation analysis of echocardiographic parameters with IRH variables in HTN patients found significant and even unpredictable associations with certain variables. Therefore, a statistically significant and moderate correlation of the ascending aortic diameter with RRI (r =0,410, p <0,01) was recorded and a statistically valid but weaker correlation with RPI (r =0,314, p <0,01) , as well as with AT (r =0,173, p <0,01) and a weak negative correlation with RV/RRI ratio (r =-0,188, p <0,01). The interdependence of the left ventricular size with IRH parameters was assessed to reveal a statistically significant positive correlation of the antero-posterior LA diameter with RRI (r =0,436, p <0,01), RPI (r =0,358, p <0,01) , as well as a negative correlation with RV/RRI (r =-0,208, p <0,01). Similarly, a significant interconnection was found between the LA volume and LA volume index with RRI (r =0,333, p <0,01) and (0,410, p <0,01), respectively, as well as with RPI (r =0,245, p <0,01) and (r =0,296, p <0,01) (Figure 6).

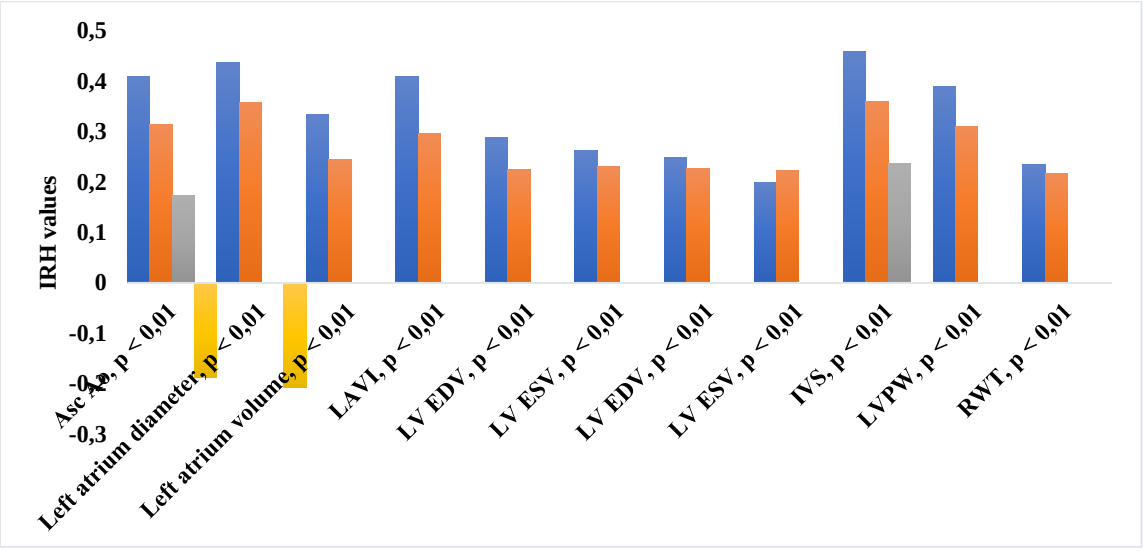

Figure 6. **Correlative analysis of IRH variables with echocardiographic parameters characterizing the left heart**

Note. p <0,01 Correlations of RRI, RPI, AT with ascending aorta diameter, left atrium, left atrium volume, left atrial volume index, left ventricular diastolic and telesistolic dianeters and volumes, interventricular septum thickness and left ventricular posterior wall thicknessrelative wall thickness.

Valid significant clinical and statistical ratios of IRH parameters with LVM and LVMI were found, thus LVM and LVMI with RRI (r =0,449, p <0,01) and (r =0,468, p <0,01) were the most significant data, then less important for RPI (r =0,373, p <0,01) and (r =0,355, p <0,01), and the lowest values for AT (r =0,223, p <0,01) , (r =0,247, p <0,01) (Figure 7).

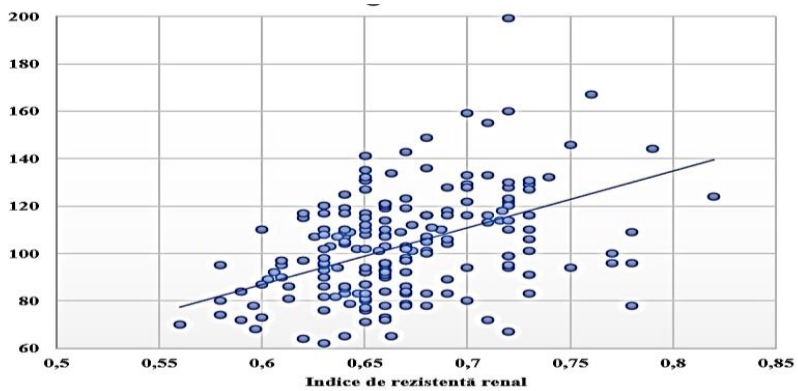

Figure 7. Correlations between LVMI and RRI

Note. p <0,01 - RRI differences according to LVMI

Significant affinity was reported for IRH parameters and LV geometry, the highest RRI values being recorded in patients with dilatated concentric LV hypertrophy, followed by dilated eccentric hypertrophy, then non-dilated eccentric type, non-dilated concentric , whereas the lowest RRI values were found in patients with no LV hypertrophy (0,688 vs 0,678 vs 0,675 vs 0,673 vs 0,647, p <0,01). Similar data were found for RPI with the lowest values in cases without hypertrophy and the highest values in dilatated concentric LV hypertrophy (1,178 vs 1,244 vs. 1,246 vs 1267 vs 1,345, p <0,05) and AT (65,04 vs 66,90 vs. 67,90 vs 67,99 vs 69,01, p <0,001),

respectively. No significant differences were revealed in LV geometry for RV and RV/RRI (Table 2).

Table 2. Comparative analysis of IRH parameters depending upon LV geometry.

	Dilated concentric	Non-dilated concentric	Dilated eccentric	Non-dilated excentric	No hypertrophy	p
RRI	0,69	0,67	0,68	0,68	0,65	<0,01
RPI	1,35	1,27	1,25	1,24	1,18	<0,05
AT	68,01	66,94	67,99	67,90	65,40	<0,001
RV	107,75	128,07	123,00	135,00	132,92	>0,05
RV/RRI	157,00	192,94	184,40	193,53	205,54	>0,05

Note. *RRI – renal resistive index; RPI – renal pulsatile index; AT – Acceleration time; RV – renal volume*

It was found that almost all IRH parameters had very high affinity for the presence of diastolic dysfunction, while RRI values were considerably higher in patients with signs of diastolic dysfunction of the LV (0,627 vs 0,676, p <0,001), as well as RPI (1,146 vs 1,265, p <0,001) and AT (65,113 vs 67,003, p <0,001), no statistically significant differences were found for RV depending on the presence of diastolic dysfunction, and in the case of RV/RRI there were higher values in the absence of diastolic dysfunction of the LV (215,457 vs 188,124, p <0,001), (Figure 8).

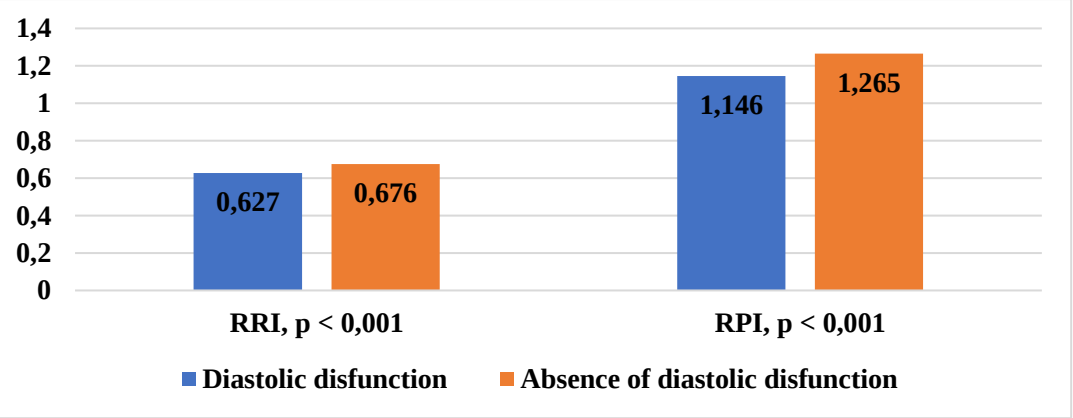

Figure 8. **RPI and RRI values depending on the presence of LV diastolic dysfunction.**
Note. p <0,001 - differences between RRI, RPI, depending on the presence of left ventricular diastolic dysfunction.

2.4 The nictemeral HTN variability and affinity of the nictemeral HTN patterns to IRH parameters.

The study of nictemeral HTN patterns revealed four major phenotypes: dipper, non-dipper, reverse-dipper and extreme-dipper. according to SBP data, 2% of the studied population were assessed as night-peakers, 47,5%- non-dippers, 47% were dippers and 3,5 % - extreme dippers. The analysis of DBP variatiations included 1,5% of night-peakers, 46,5% - non-dippers, 40,5% - dippers and 11,5% of patients were assessed as extreme dippers.

The comparative analysis of nictemeral SBP and DBP variations with IRH parameters revealed that IRH parameter changes depend upon the detected HTN pattern. Thus, RRI recorded the highest values in night-peakers, followed by non-dippers, dippers, whereas the lowest being in extreme dippers. Similar corelations were assessed for RPI and AT with the highest values of RPI in night peakers and the lowest values for dippers, whereas the RV and VR/RRI ratio revealed the lowest values in night-peakers and the highest in extreme-dippers (Table 3).

Table 3. Comparative analysis of nictemeral SBP variations with IRH parameters

	Night-peaker		Non-dipper		Dipper		Extreme-dipper		p
	M	m	M	m	M	m	M	m	
IRR	0,67	0,02	0,67	0,01	0,66	0,01	0,66	0,02	>0,05
IPR	1,29	0,06	1,26	0,02	1,23	0,02	1,27	0,09	>0,05
TAR	67,87	0,13	66,54	0,26	66,82	0,27	65,86	1,03	>0,05
VR	124,67	16,18	129,93	2,43	127,73	2,69	150,00	10,97	>0,05
VR/IRR	189,67	25,18	193,71	4,27	195,51	4,24	222,42	19,97	>0,05

Note. *RRI – renal resistive index; RPI – renal pulsatile index; AT – acceleration time; RV – renal volume.*

The comparative analysis of HMOD parameters, LVMI and the indexed volume of the LA with SBP nictemeral variability patterns showed statistically significant differences in LVMI values that depend upon the assessed profile. Thus, the highest values for LVMI were found in patients with night-peaker patterns, followed by non-dippers and the lowest in extreme-dippers (105,75 vs 104,149 vs 102,247 vs 100,286, p <0,05); the assessement of IMT in both CCA and ICA showed the highest values for both CCA and ICA variables in patients with night-peaker patterns, whereas the lowest CCA values were found in dippers (1,1 vs 1,074 vs. 1,021 vs 1,057, p <0,05). No statistically significant data were found for LA, GFR and fasting glucose, however, a thorough analysis revealed the predominance of non-dipper pattern for both SBP and DBP in patients with dysglycemia (Figure 6).

The selective analysis of LVMI, IMT CCA and IMT ICA, and fasting glucose with nictemeral DBP variations revealead similarities with SBP variability, whereas a statistically significant impact was found in case of GFR. Therefore, the lowest GFR values were registered in patients with non-dipper pattern, followed by dippers and extreme-dippers, whereas the higest RFG values were assessed in night -peakers, thus providing a potential explanation for identifying patients in CKD hyperfiltring stage.

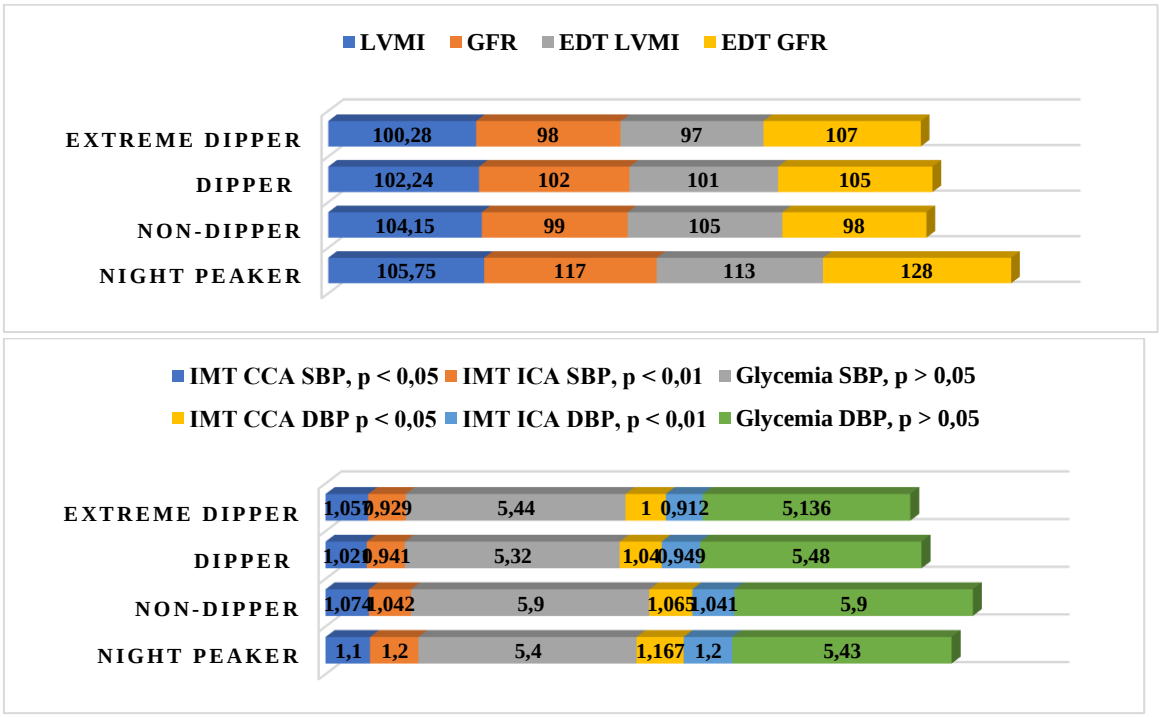

Figure 6. Comparative study between the nictemeral SBP variations with HMOD parameters and fasting glucose.

Note. p <0,05 differences LVMI, IMT CCA according to the nictemeral patterns of DBP and SBP; p <0,01 GFR differences, IMT ICA depending on the nictemeral patterns of DBP and SBP; p >0,05 glycaemia differences according to the nictemeral patterns of DBP and SBP.

2.5 The association between carotid and intrarenal haemodynamic parameters and the severity of carotid atherosclerosis in HTN.

The analysis of IRH parameters in carotid atherosclerosis, characterized by presence of plaques in CCA and ICA, revealed statistically and clinically significant findings. Significantly higher RRI values were found in patients with atherosclerotic plaques on both CCA (0,657 vs 0,687, p <0,001) and ICA levels (0,663 vs 0,710, p <0,01). Furthermore, higher RPI values were found in patients with atherosclerotic plaque on CCA (1,208 vs 1,322, p <0,05) and ICA (1,227 vs 1,448, p <0,01).

Similar association of atherosclerotic plaque on ICA with CCA and ICA diameters, as well as with velocimetric parameters on ICA and CCA did not reveal any statistically valid differences for these variables. Moreover, the comparative study of atherosclerotic plaques on ICA with CRI found statistically significant differences for both RCI on CCA (0,800 vs 0,850, p <0,01) and for RCI on ICA (0,746 vs 0,764, p <0,05), a phenomenon that had been registered for IMT on CCA (1,033 vs 1,158, p <0,05) and IMT on ICA (0,968 vs 1,121, p <0,01).

The study of IRH correlation with carotid atherosclerosis revealed statistically significant RRI correlation with the IMT at both CCA (r =0,413, p <0,05) and ICA (r =0,475, p <0,05) levels, as well as a weaker, statistically authentic correlation of RPI with IMT on CCA (r =0,274, p <0,05) and ICA (r =0,289, p <0,05) levels. A similar statistically strong correlation was found when comparing AT with IMT on both CCA (r =0,291, p <0,05) and ICA (r =0,291, p <0,05) levels. No correlations of IMT with RV were found, however the study of IMT associated with RV/RRI showed statistically significant negative correlations of RV/RRI with IMT on CCA (r =-0,212, p <0,05) and on ICA (r =-0,233, p <0,05).

A similar comparative study of the carotid atherosclerosis parameters (IMT) with carotid morphological and haemodynamic parameters was carried out. The study of carotid morphology revealed strong, statistically significant correlation of IMT on CCA with CCA (r =0,532, p <0,05) and ICA diameters (r =0,394, p <0,05), as well as a valid statistical association of IMT on ICA with CCA (r =0,420, p <0,05) and ICA diameters (r =0,388, p <0,05).

2.6 Intrarenal haemodynamics in hypertensive patients depending on type of impared glucose metabolism

The general study group was divided into two groups according to the precence different types of dysglycemia. No statistically significant differences were found for IRH parameters , whereas slightly higher values were assessed for RRI and RPI within hyperglycemia-related group (0,675 vs 0,664, p >0,05) and (1,285 vs 1,231, p >0,05) and AT (66,458 vs 66,997, p >0,05), as well as statistically higher non-significant RV and RV/RRI values (124,87 vs 136,12, p >0,05) and (189,58 vs 204,05, p >0,05) were recorded in group with dysglycemia (figure 10).

In the attempt to compare the degree of atherosclerotic burden in those 4 study subgroups, there were found statistical and clinical - hemodynamic authentic differences. Thus, the highest values for CCA diameter were identified in patients with impaired glucose tolerance, followed by patients with DM, and the lowest values of CCA diameter were found in hypertensive patients without dysglycemia (7,493 vs 7,371 vs. 7,313 vs 7,02, p <0,01).

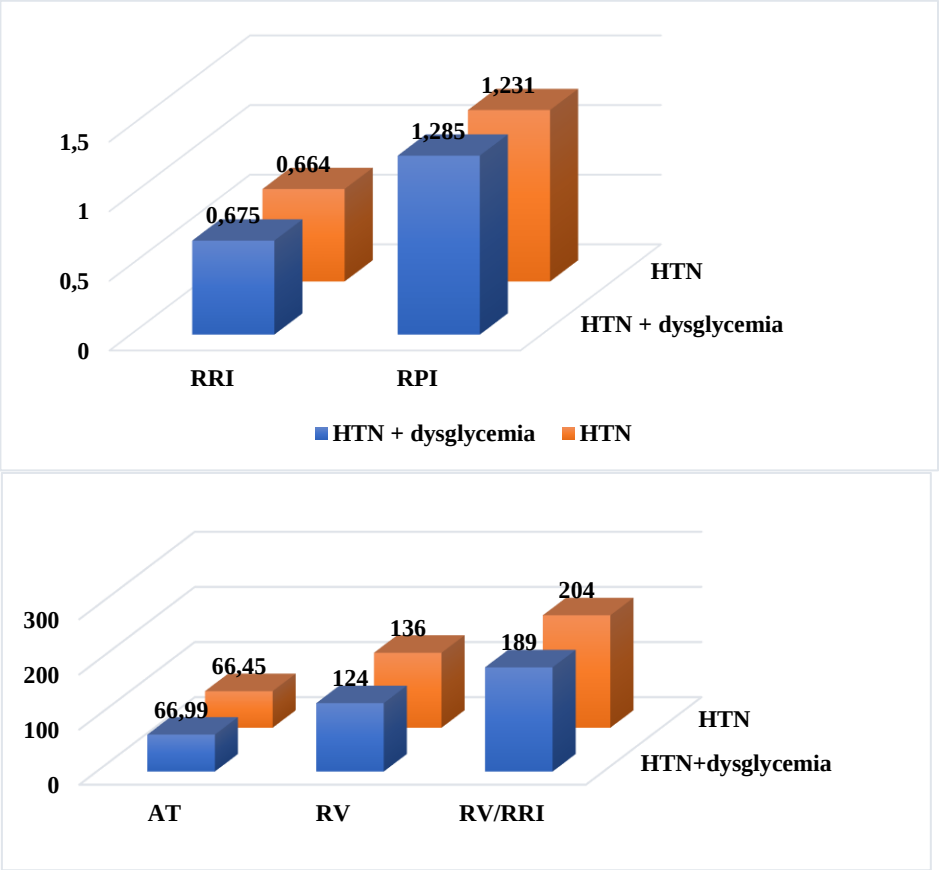

Figure 10. Differences in IRH parameters depending on the presence of dysglycemia

The comparative study of IMT among the study population revealed some remarkable observations, thus IMT assessed on both CCA and ICA showed the highest values in diabetic patients and the lowest values for hypertensive patients without dysglycemia, IGT and IFG patients exhibited medium values for IMT on CCA (1,135 vs 1,114 vs 1.064 vs 1,005, p <0,01) and IMT on ICA (1,069 vs 1,014 vs 0,974 vs 0,956, p <0,01).

Comparative analysis of the biochemical parameters including lipid and glucose profile, based on the presence and type of dysglycemia revealed statistically and clinically significant differences in basal glycaemia, total cholesterol, LDL-C, HDL-C, and triglycerides

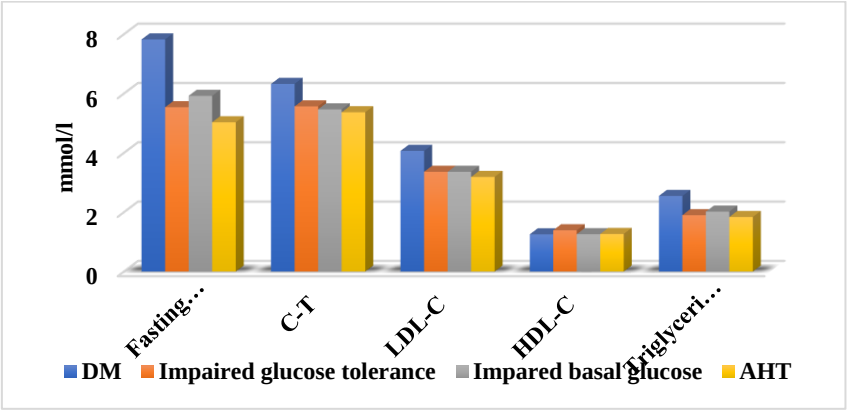

Figure 11. Particularities of lipid and glucose profile in patients from the study groups

Note. p <0,05 differences in HDL-C values depending on the type of dysglycemia; p <0,01 differences in LDL-C, TC, triglycerides depending on the type of dysglycemia; p <0,001 differences in fasting glucoze depending on the type of dysglycemia.

The comparative study of IRH among the study subgroups showed the highest RRI values in diabetic patients followed by those with IGT, IFG, whereas the lowest RRI values were registered in patients without dysglycemia (0,694 vs 0,667 vs 0,666 vs 0,664, p <0,05). Similar valid statistical data were reported for RPI (1,352 vs 1,224 vs 1,262 vs 1,173, p <0,01). AT, RV and RV /RRI values did not reveal any statistical authentic significance.

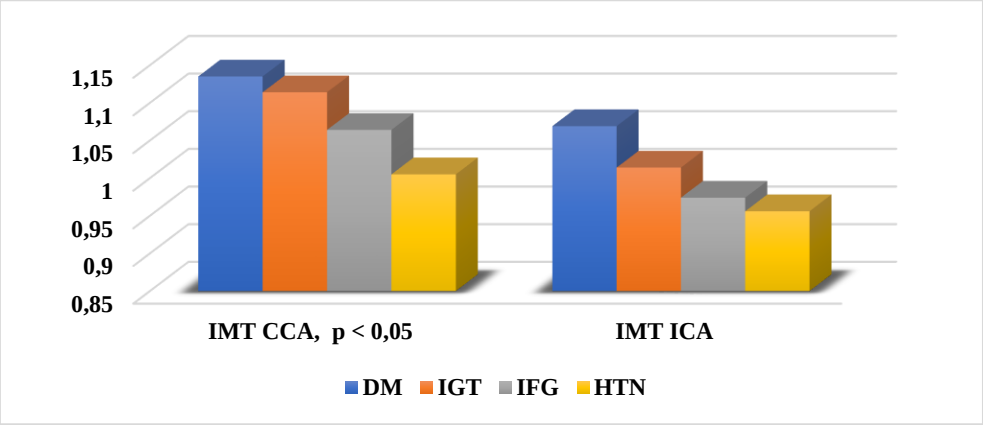

Figure 12. **IMT particularities depending on the presence and types of dysglycemia**
Note. p <0,05 IMT CCA differences depending on the presence and type of dysglycemia; p <0,001 IMT ICA differences depending on the presence and type of dysglycemia.

2.7 Assessment of intrarenal hemodynamics depending on microvascular and macrovascular damage in patients with dysglycemia and HTN

The estimated interconnection of IRH parameters with variables of microvascular disease in patients with HTN and dysglycemia depending on impaired glucose metabolism revealed some significant, statistical and clinical regularities.

Patients with dysglycemia associated with HTN were distributed into 3 groups, depending on the type dysglycemia, thus we obtained the following categories: first group of patients with DM, the second group of patients with IGT and the third group included patients with IFG.

The analysis of IRH parameters with macrovascular disease variables in the group of diabetic patients showed statistically positive authentic correlations between RRI and PP (r =0,495, p <0,01), RPI and PP (r =0,478, p <0,01), as well as statistically valid negative correlations between RV/RRI and PP (r =-0,352, p <0,01). Similarly, statistically high, positive and authentic affinity was recorderd between IRH and IMT on CCA and IMT on ICA, including correlation between RRI and IMT on CCA (r =0,422, p <0,01) and IMT on ICA (r =0,440, p <0,01), RPI and IMT on CCA (r =0,294, p <0,05). However, no correlation was found between RPI and IMT ICA, whereas a statistically true negative correlation was estimated regarding for RV/RRI and IMT on CCA and IMT on ICA, as follows: RV/RRI and IMT on CCA (r =-0,354, p <0,01) , RV/RRI and IMT on ICA (r =-0,346, p <0,01).

The comparative assessment of IRH parameters with peripheral vascular damage by ABI, revealead significantly higher RRI values in group of patients with DM and peripheral vascular disease compared to those with the borderline ABI markers and without peripheral arterial disease 0,715 vs 0,683 vs 0,65, p <0,001), being valid for RPI, as well (1,384 vs 1,335 vs 1,199, p <0,001). However, a concomitant, reverse relationship beween RV/RRI and ABI was registered, with the highest values of RV/RRI assessed in patients with normal ABI, then lower values in those with borderline ABI , the lowest being in patients with PAD (216,8 vs 204,53 vs 161,75, p <0,01).

The parameter assessment of microvascular damage associated with hypertensive disease and impaired glucose metabolism, showed both statistical and clinical significance. Therefore, the study of relationships between IRH parameters in both hypertensive and diabetic retinopathy, recorded significantly higher RRI values in patients with both hypertensive (0,689 vs 0,651, p <0,001) and diabetic retinopathy (0,695 vs. 0,655, p <0,001); significantly higher values were found for RPI in patients with both hypertensive (1,357 vs 1,174, p <0,001) and diabetic retinopathy (1,354 vs 1,243, p <0,01); the highest values were recorded for RV and RV/RRI in patients without hypertensive retinopathy (129,37 vs 143,25, p <0,05) for RV and (185,34 vs 218,09, p <0,01) for RV/RRI, respectively, as well as in patients with diabetic retinopathy with maximal RV/RRI values in patients without retinopathy (214,92 vs 186,45, p <0,01).

The comparative study of IRH parameters depending on hypertensive retinopathy grading showed the highest RRI values in patients with grade III hypertensive retinopathy, then lower values for grade II retinopathy and grade I hypertensive retinopathy, respectively (0,746 vs 0,711 vs 0,669, p <0,001). Similar data were found for RPI (1,725 vs 1,364 vs 1,287, p <0,001) and opposite correlations were observed for RV/RRI ratio, with the highest values in patients with grade I hypertensive retinopathy and the lowest in patients with grade III retinopathy. Statistically significant laws have been set for diabetic retinopathy, with maximum values of IRH parameters in patients with the highest grade of retinopathy, though, due to a low number of patients of each grade of retinopathy, we consider these results not worthy of being reported.

Furthermore, reliable statistical ratios between RRI and diabetic neuropathy were found resulting from the comparative assessment of IRH parameters with presence and grading of diabetic neuropathy due to dysglycemia-related microvascular damage. Thus, the highest RRI values were registered in patients with diabetic neuropathy compared to those without neuropathy (0,702 vs 0,658, p <0,001), the same findings being found for RPI (1,358 vs 1,227, p <0,01), and reversed indicators for RV/RRI ratio with maximum VR/IRR values in patients without neuropathy (216,6 vs 183,7, p <0,01).

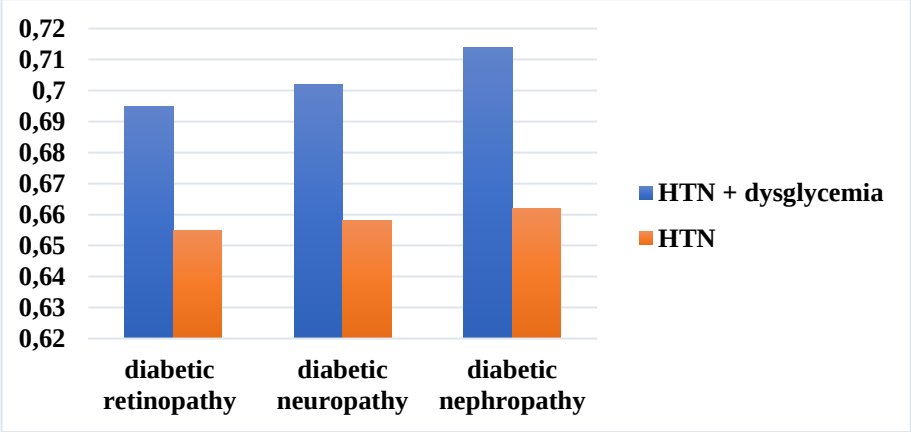

Figure 13. RRI depending on the presence of dysglycemia and microvascular complications

Note. p <0,001 RRI differences depending on the presence of diabetic retinopathy, diabetic neuropathy and diabetic nephropathy.

Statistically true, positive correlations were found in study of the affinity of some other parameters of macrovascular damage in HTN, namely IMT on CCA and IMT on ICA with IRH variables. Positive correlation were found between IMT on CCA and RRI (r =0,320, p <0,01), RPI (r =0,204, p <0,05), and AT (r =0,251, p <0,05), as well as for IMT on ICA and RRI (r =0,408, p <0,01), PI (r =0,329, p < 0,01), and AT (r =0,389, p <0,01). Simultaneously, negative correlations

were recorded between IMT on CCA and IMT on ICA with RV and RV/RRI, having the lowest statistical power.

Comparative assessment of IRH parameters with markers of microvascular damage in hypertensive patients revealed statistically significant negative correlations between RRI and GFR ($r = -0,215$, $p < 0,01$), whereas no significant correltions were found for other IRH variables and GFR within this group. When comparing IRH values in presence of hypertensive retinopathy, we found significantly higher RRI values (0,682 vs 0,652, $p < 0,001$) and higher RPI values in patients with retinopathy (1,28 vs 1,197, $p < 0,01$), as well as higher RV/RRI values in patients without retinopathy (195,69 vs 178,54, $p < 0,01$). Whereas the assessment of IRH variables based on grading of retinopathy exhibited the highest RRI values in patients with grade III retinopathy and lower values for those with grade II and I retinopathy (0,718, vs 0,689 vs 0,669, $p < 0,01$). Other IRH parameters revealed no statistically true relationships, however similar regularities as in abovementioned maintained, with maximum RPI and AT values in patients with grade III retinopathy and minimum values for patients with grade I retinopathy, as well as diametrically opposed data for RV and RV/RRI.

Due to multiple studies, a significant relationship between IRH parameters and microvascular and macrovascular impairment was assessed within CV disorders such as HTN and dysglycemia. Furthermore, the cumulative risk assessment reported that diabetic patients were at highest risk of developing vascular damage (both microvascular and macrovascular impairment), showing the highest values for RRI and PI.

Considering the obtained study outcomes, we can assert that IRH has a strong and significant correlation with both systemic vascular damage and microcirculation, being in the center of this relationship, thus we can assume that IRH parameters represent the potential link between the microcirculation and systemic macrovascular bed.

SUMMARY OF THE OBTAINED RESULTS

IRH parameters may have a potential impact in assessing the most heterogeneous groups of hypertensive patients. Moreover, essential HTN-associated IRH may reflect the CKD progression beyond the glomerulopathy-related conventional determinants, as well as with a possible CV risk factors and prognosis. Therefore, even if IRH parameter assessment is considered a simple one, it requires limited competencies and has significant reproducibility. These parameters can be defined as useful and multifunctional tools, providing a deeper insight into CV disease continuum, global CV risk factors, and kidney involvement in hypertensive patients.

The existing data collection and our obtained research data prove that IRH parameters might have a remarkable potential impact in assessing both hypertensive patients and patients with different types and grades of impaired glucose metabolism. However, further studies are required to clear up a number of related uncertainties. First, there is no consensus on assessment of the exact site of the highest IRH parameters, thus diferent studies describe various sites such as segmental, arcuate or interlabial arteries. Another issue we have tried to partially solve out was the individual impact of major and small vessels on changes in IRH values. Referring to kidney microvascular impairment and its potential impact on IRH, it is still unclear which of the three renal microvascular beds show the highest affinity for IRH variability. Other two major concerns would be the impact of lifestyle changes on IRH variables in patients with modifiable risk factors, HTN and dysglycemia, and and the potential role of the IRH variables on CV prognosis regarding the CV morbidity, studied within large cohorts of patients.

Our research has contributed to the strengthening of the evidence-base for complex interaction of systemic microcirculation and renal microvascular disease with systemic macrovascular parameters such as vascular rigidity, atherosclerotic burden and remodeling of major heart vessels, being integrated into an intricate and well-organized universe of significant mutual correlations [24]. Intravascular Resistance analysis may be useful in vascular assessment of the patient, providing information on both microvascular and macrovascular impairment, inferring the idea that it is an indirect parameter of vascular rigidity and of possible atherosclerotic impairment in patients with HTN and dysglycemia. Moreover, the association between IRH and vascular damage may indicate an early renal small-vessel involvement, in most cases requring therapeutic interventions before irreversible vascular damages establish.

Although our study included reasonable patient cohorts with acceptable homogeinity, it has limitation of being cross-sectional and transversal. Therefore, there is no data on the evolution of the temporal axis of the studied parameters. Longitudinal studies and those requiring therapeutic interventions should be conducted in order to confirm the utility of IRH parameters as independent CV risk factors.

CONCLUSIONS AND RECOMMENDATIONS

GENERAL CONCLUSIONS

1. Correlations of intrarenal haemodynamics variables with anthropometric, hemodynamic and asymptomatic target organ damage in hypertensive patients were of particular significance, with major emphasis on associations of renal resistance index and pulsatility index with degree and type of obesity, blood pressure values, hypertensive retinopathy and vascular remodeling parameters.
2. Significant correlations were reported for renal resistive index with carotid hemodynamic parameters, especially with the carotid wall thickness and carotid atherosclerotic burden within common and internal carotid arteries, a fact, which highlights the affinity of renal hemodynamic impairment vs the severity of systemic atherosclerosis, thus suggesting a direct relationship of intrarenal hemodynamics with systemic vascular damage in HTN.
3. The study of nictemeral HTN profiles in hypertensive patients highlighted the importance of insufficient decrease in blood pressure overnight (night-picker and non-dipper pattern), which influenced the intrarenal hemodynamic parameters, vascular rigidity, carotid atherosclerosis and remodeling, hypertensive nephropathy and cardiac hypertrophy with a particular expression of these phenomena in profound impaired glucose metabolism.
4. The study of correlations between intrarenal hemodynamic parameters and echocardiographic data revealed inseparable and valid relationships among renal resistance index with type and degree of left atrial and ventricular remodeling, presence and degree of diastolic dysfunction of LV, as well as with the variables of right ventricular function and remodeling.
5. The presence of diabetes in hypertensive patients significantly increases the affinity of intrarenal hemodynamics for both microvascular (retinopathy, nephropathy, neuropathy) and macrovascular impairment (vascular rigidity and atherosclerotic burden), echocardiographic parameters of atrial and ventricular remodeling (left and right) and their degree of expression.
6. Among the intrarenal hemodynamics parameters, the renal resistence index showed a strong and valid correlation with both systemic or microvascular vascular impairment and asymptomatic target organ damage, thus validating the hypothesis on the potential role of renal resistance index as an additional marker of target organ damage in HTN.

PRACTICAL RECOMMENDATIONS

1. Routine use of additional assessment techniques of HMOD in patients with HTN, as well as in those with dysglycemia in order to estimate the CV risks and ensure prompt interventions before complications establish.
2. Recommendation on ABPM in all hypertensive patients with HTN, especially in presence of HMOD. Presence of pathological nictemeral profile (“non-dipper", "night-picker") requiring efficient interventions, which would restore the circadian variability of the tension values in order to improve prognosis.
3. Modified Doppler techniques, used on both renal arteries and carotid vessels with consistent reporting of intrarenal and carotid hemodynamics in order to assess the systemic influence of recorded haemodynamic patterns.
4. Conventional usage of IRH parameters and, particularly of RRI in assessment of HTN patients and different degrees of impairment of glucose metabolism.
5. It is worth considering RRI as an original and fundamental surrogate parameter in patients who accumulate CV risk factors, followed by their proper distribution into different therapeutic intervention groups.
6. Practical recommendations based on the present study data are addressed to family doctors, internists, imagind specialists and cardiologists.

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- **Articles published in foreign scientific journals:**

✓ **Summaries in ISI, SCOPUS and other international databases ***

8. **Cabac-Pogorevici I.,** Revenco V. Renal resistive index: general and hemodynamic determinants in hypertensive patients. *Journal of Hypertension (Supplement. European Society of Hypertension 2018 Abstract Book*). 2018; vol 36, 165 **(IF 4,099)**
9. **Cabac-Pogorevici I.,** Revenco V. Upper limb vein thrombosis and pulmonary embolism in a HIV infected patient. *European Journal of Heart Failure*. 2018; 20 (Suppl. S1), 177. doi:10,1002/ejhf.1197 (**IF 10, 683)**
10. Cabac-Pogorevici I., Revenco V. Renal and carotid resistive indexes – the same matter with different layout? *European Heart Journal – CV Imaging*, 2018; December, 1396 **(IF 8,336)**

11. Mihalache G., Ochişor V., **Cabac-Pogorevici I.,** Revenco V. Imidazolinic i1 receptors agonist – monoxidine in the treatment of the pICAents with diabetes mellitus in association with arterial hypertension, *Interdiab 2016* (ISI Thompson Reuters Database)

- **Summary / abstract / thesis within national and international scientific conferences**
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    12. **Cabac-Pogorevici I**. PICAenta cu Hipertensiune arterial și afectare de organ țintă. Caz clinic. Grand Courses 2017. *Conferință Comuna a Societății Europene de Cardiologie și Societății de Cardiologie din Republica Moldova,* 2017

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    16. **Cabac-Pogorevici I.** Ultrasonografia abdominală în diagnosticul afectării viscerale la pICAenții cu sindrom metabolic. *Conferința științifică anuală a colaboratorilor și studenților. Culegere de rezumate științifice. Zilele Universității de Stat de Medicină și FarmICAe* „Nicolae Testemițanu", 2015,
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    18. **Cabac-Pogorevici I.** Caz clinic. Grand Courses 2017. *Conferință Comuna a Societății Europene de Cardiologie și Societății de Cardiologie din Republica moldova*, 2017 (Prezentare).
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    22. **Cabac-Pogorevici I.** Evaluarea și conduita pICAentului cu afectarea valvei aortice. *Simpozion. Actualități în cardiologie prin prisma ghidurilor noi ale Societății Europene de Cardiologie 2017. Zilele Universității de Stat de Medicină și FarmICAe „Nicolae Testemițanu,* 2017
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- **Poster presentations within scientific forums:**
  - ✓ **International participation**
    27. **Cabac-Pogorevici I.** Renal and carotid resistive indexes and left ventricular remodelling in arterial hypertension. *ECR 2019*
    28. **Cabac-Pogorevici I.** Intrarenal hemodynamics and left ventricular geometry in patients with arterial hypertension. *ECR 2018* C-0024 http://dx.doi.org/10,1594/ecr2018/C-0024
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- **Informative scientific works:**
    36. Pop-Moldovan A., Trofenciuc N.M., Pușchița M, Dărăbanțiu D.A., Mercea S., Hreniuc C., F. Onel M., Revenco V., **Cabac-Pogorevici I.,** Tomescu M.C., Branea H., Christodorescu R. New biomarkers in screening anthracycline induced cardiotoxicity only with peripheral blood sampling. *InTechOpen Book*, 2018
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