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HEMODYNAMIC IMBALANCE – A PREDICTOR OF SUBOPTIMAL BLOOD PRESSURE CONTROL IN A HYPERTENSIVE POPULATION FROM A HIGH CARDIOVASCULAR RISK COUNTRY

Abstract. *The scope of this study was to assess the hemodynamic (HD) profile of a hypertensive population and to explore its possible role in hypertension control, using the data from a national-representative survey. Impedance cardiography was performed in 771 adult hypertensive subjects, randomly selected from SEPHAR III survey's database. Analysis of impedance cardiography recordings showed a variety of 22 different HD profiles. Only 6.2% of the screened*

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subjects had a normal HD profile. Antihypertensive treatment seems to be unrelated to HD profile. Regression analysis revealed a positive association between the number of altered HD modulators and the lack of BP control. Our findings emphasize the need for HD profile assessment when choosing the most appropriate antihypertensive drug for each patient. Disregarding the HD profile may lead to hemodynamic imbalance and suboptimal blood pressure (BP) control.

Keywords: *blood pressure, control, hemodynamic modulators, impedance cardiography, hypervolemia, treatment, survey, non-invasive.*

JEL Classification: I10

1. INTRODUCTION

Arterial hypertension (HT) continues to be the leading cause of death worldwide, with a currently estimated global hypertensive population of approximately 1billion individuals that is expected to rise up to 1.56billion by the year 2025 [1-3].

According to the latest national-representative survey – SEPHAR III (Study for the Evaluation of Prevalence of Hypertension and Cardiovascular Risk), 4.5out of 10 Romanian adults are hypertensive and HT prevalence is expected to be of about 44% by year 2020, based on the trend of HT prevalence revealed by the three SEPHAR surveys over the last 11 years [4].

Despite major advances in antihypertensive pharmacological and interventional treatment, optimal BP control rate is difficult to achieve not only in our country but worldwide [4-9].

According to the current international guidelines, HT treatment is guided by BP values as well as the estimated total cardiovascular (CV) risk and the presence of comorbidities. At least, two antihypertensive drugs that have additional CV protective effects are recommended [5,10]. However, this strategy seems not to be enough to reach optimal BP control in hypertensive patients and makes us wonder where are we wrong?

If we go back to the pathophysiology of this disease and look upon the hemodynamic aspect, we acknowledge that adequate oxygen delivery (DO2) to all tissues is the primary function of the cardiovascular system [11,12].

The oxygen delivery state is modulated by perfusion blood flow that is characterized by the cardiac index (CI). Cardiac index is expressed as the product between the stroke index (SI) and heart rate (HR). The stroke index that defines the hemodynamic state is influenced by cardiac contractility, through intravascular volume and inotropism, and by vasoactivity, while HR is influenced by cardiac chronotropism. Therefore, the 4 major hemodynamic modulators of O2 delivery state are intravascular volume (volemia), inotropism, vasoactivity and chronotropism [11,12].

The hemodynamic state of a patient can be graphically expressed as a point on a hemodynamic map having stroke index(SI) on horizontal axis and mean arterial blood pressure (MAP) on vertical axis. Hemodynamic modulators (intravascular volemia, inotropism and vasoactivity) can be graphically expressed in the diagonal system of lines on the same map. Stroke Systemic Vascular Resistance Index (SSVRI) evaluates vasoactivity and Left Stroke Work Index (LSWI) evaluates total contractility as the sum of inotropy and intravascular volemia [11, 12].

There are nine classes of hemodynamic states into which the hemodynamic point of a patient can fall, but only one of them, called the normal hemodynamic state, can serve as the therapeutic goal. A normal hemodynamic state implies a simultaneous normal MAP and normo-dynamic stroke index(SI) [11,12].

Essential hypertension is the result of alteration in any of the following hemodynamic modulators (or any combination between them): hypervolemia, hyperinotropism and/or vasoconstriction [13.14].

In daily practice it is impossible to predict which hemodynamic modulator is altered and in what amount, without a non-invasive hemodynamic evaluation.

From a hemodynamic perspective, each hypertensive patient needs an individualized treatment in order to achieve optimal blood pressure control. However, in clinical practice, the choice of a specific antihypertensive drug does not take into consideration the individual hemodynamic profile of the patient. Administration of inappropriate antihypertensive drug classes and/or dosage may lead to hemodynamic imbalance, treatment failure and resistance to treatment. A mismatch between the chosen antihypertensive drug and patient's hemodynamic profile may be one of the causes of inadequate blood pressure control. The optimal selection of specific drug classes and/or dosage could be better achieved by assessing the hemodynamic profile of each hypertensive patient (MAP&SI) [14-18].

The scope of this study was to evaluate the HD profile of a sample of adult Romanian hypertensive population through impedance cardiography and to explore its possible role in HT control in the frame of the national-wide SEPHAR III survey.

2. METHODS

Detailed SPEHAR III survey's methodology was previously published elsewhere [4,19].Only the relevant aspects for the current analysis will be presented.

2.1 Study sample

Among the 1970 Romanian adults enrolled in SEPHAR III survey, 889 subjects were identified as being hypertensive (either previously known or newly diagnosed) [4], out of which 771 had valid data from non-invasive hemodynamic measurements (Figure 1) representing the current study sample.

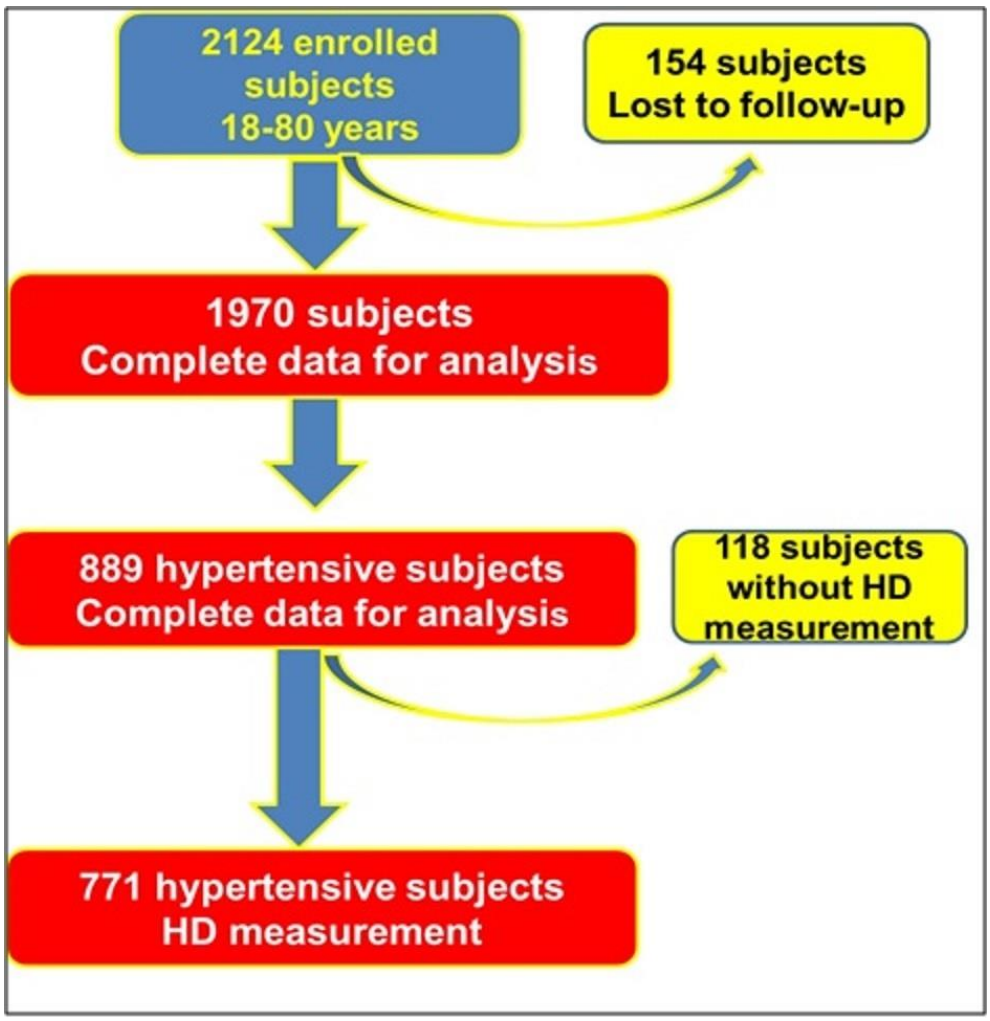

Figure 1: Study sample selection from SEPHAR III data base. HD: hemodynamic

2.2 Blood pressure measurements

Three BP measurements taken 1 minute interval in seated position were performed during each study visit using an automated oscillometric BP measuring device certified by Association for the Advancement of Medical Instrumentation (AAMI), European Society of Hypertension(ESH) and British Hypertension Society(BHS) (OMRON M6 AC), according to current ESH-ESC guidelines [4.19].

2.3 Hypertensive state was defined by systolic blood pressure (SBP) ≥ 140mmHg and/or diastolic blood pressure (DBP) ≥ 90mmHg at both study visits, using the arithmetic mean of the second and third BP measurement of each study visit (without taking into consideration the first BP measurement from either visit), or previously diagnosed HT under treatment during the previous two weeks, regardless of BP values [4,19].

2.4Blood pressure control was defined as SBP < 140mmHg and DBP < 90mmHg in hypertensive subjects who were under treatment for at least 2 weeks before, taking into account the maximum value between the two SBP/DBP values from each visit [4,19].

2.5 Adherence to antihypertensive therapy was evaluated by 4-item Morisky medication adherence scale (MMAS-4) [20-22].

2.6 Salt intake was estimated as follows: for every 100mmol/day Na excretion (estimated
by Kawasaki formula [23], using sodium excretion values measured from the morning spot sample) corresponds to 5.8g/day NaCl intake.

2.7 Non-invasive hemodynamic measurements

Non-invasive hemodynamic measurements were performed by bio-impedance cardiography using HOTMAN ® System, during the second study visit.

Bioimpedance refers to the tissue resistance when crossed by high frequency and low magnitude electrical current. The method relies on the fact that blood is the best electrical conductor in the human body. The current generated by a pair of specially design electrodes placed in the upper clavicular area is therefore forced to pass on its way to the through the receptor electrodes, placed in the lower part of the thorax, through the lowest resistance area, that is through the thoracic aorta). Having a simultaneous ECG signal recording the HOTMAN ® System will record beat-to-beat variation of the bioimpedance of the aorta. All the other hemodynamic parameters will be thereafter calculated by the specially design software of the system (Figure 2).

Measurements were performed for 5-10 minutes in supine position, with estimates of volemia, vasoreactivity, inotropism and hemodynamic state, obtained over a minute during which the HD profile was stable and all the received signals (ECG, bioimpedance and respiration rate) were of good quality.

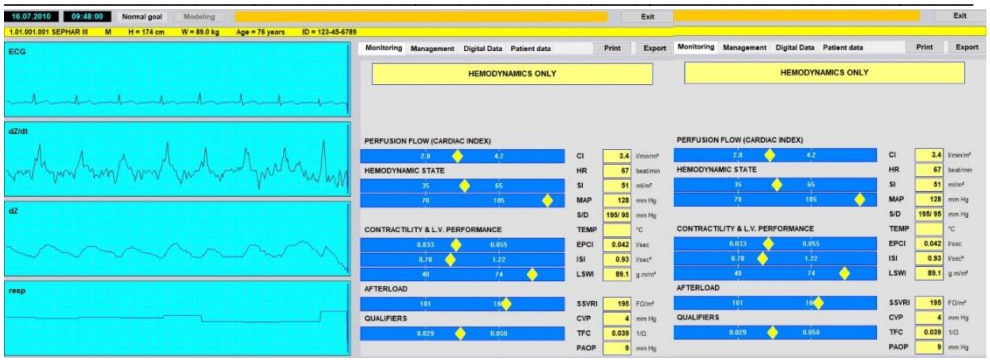

Figure 2.Output of the non-invasive hemodynamic measurement with HOTMAN ® System of a subject from the study sample.

2.7 Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 20.0 software at a significance level of $p \leq 0,05$. A descriptive analysis (means, medians, standard deviation and range for continuous data and frequency analysis for categorical data) and inferential analysis using independent samples t-test or Mann-Whitney U test for differences between means of 2 independent groups, bivariate correlation analysis and binary logistic regression using stepwise likelihood ratio method, with adjustments form major confounders and collinearity analysis, was performed.

3. RESULTS

General characteristics of the study sample are detailed in Table 1.

Table 1. General characteristics study sample

	WG N = 771	Uncontrolled HT N= 603	Controlled HT N = 168	p
Distribution by genders:				
• Feminine	369 (47.9%)	101 (27.4%)	268 (72.6%)	11<0.0001*
• Masculine	402 (52.1%)	67 (16.7%)	335 (83.3%)	<0.0001*
Age (years)	55.72±15.58	47.6±17.59	57.99±14.18	NS**
Distribution by age categories				
• 18-39 years	125 (16.2%)	60 (48%)	65 (52%)	<0.0001*
• 40-59 years	281 (36.4%)	57 (20.3%)	224 (79.7%)	<0.0001*
• 60-80 years	365 (47.3%)	51 (14%)	314 (86%)	<0.0001*
Distribution by area of residence				
• Rural	314 (40.7%)	59 (18.8%)	255 (81.2%)	<0.0001*

	WG N = 771	**Uncontrolled HT N= 603**	**Controlled HT N = 168**	**p**
• Urban	457 (59.3%)	109 (23.9%)	348 (76.19%)	<0.0001*
SBP (mmHg)	139.59±21.29	121.49±13.91	144.63±20.22	<0.0001***
DBP (mmHg)	83.37±11.77	74.73±9.62	85.77±11.18	<0.0001***
MAP (mmHg)	102.10±13.79	90.35±9.91	105.38±12.941	<0.0001***
HR (bpm)	73.16±17.61	70.94±14.73	73.78±18.29	NS**
Obesity • **BMI≥30kg/m2** • **Abdominal obesity**	 361 (46.8) 650 (84.3)	 45 (12.5) 113 (17.4)	 316 (87.5) 537 (82.6)	 <0.0001* <0,0001*
Smoking	149 (19.8)	41 (27.5)	108 (72.5)	<0,0001*
Dyslipidemia	642 (83.3)	123 (19.2)	519 (80.8)	<0.0001*
DM	128 (16.6)	16 (12.5)	112 (87.5)	<0.0001*
Salt intake	13.15±4.16	11.72±3.93	15.56±4.13	<0,0001**
Antihypertensive drugs				
ACEIs	251 (45.3)	142 (56.5)	109 (43.5)	<0.0001*
ARBs	60 (10.8)	37 (61.7)	23 (38.3)	<0.0001*
Diuretics	258 (46.6)	149 (57.8)	109 (42.2)	<0.0001*
BBs	219 (39.6)	165 (75.3)	54 (24.7)	<0.0001*
CCBs	104 (18.7)	81 (77.8)	23 (22.2)	<0.0001*
CAAs	16 (2.9)	9 (56.2)	7 (43.8)	NS*

*Values are present as absolute number (percent) for categorical variables and as mean ± standard deviation for scale variables; WG: whole study group; HT: hypertension; N: total number of subjects; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial blood pressure; HR: heart rate, bpm: beats per minute; BMI: body mass index, DM: diabetes mellitus, ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptors blockers, BBs: beta-blockers, CCBs: calcium channels blockers, CAAs: centrally active antihypertensives, *chi square test, **Mann-Whitney U test, *** independent samples t test; NS: non-statistical significant (p ≥0.05).*

Although the majority of hypertensive subjects were treated (554 cases,71.9%) in their majority with at least 2 antihypertensive drugs (59.6%), optimal BP values were recorded in only 168 (30.3%) of treated patients.

The recorded hemodynamic state of each hypertensive subject in the study sample is represented on the hemodynamic map in Figure 3.

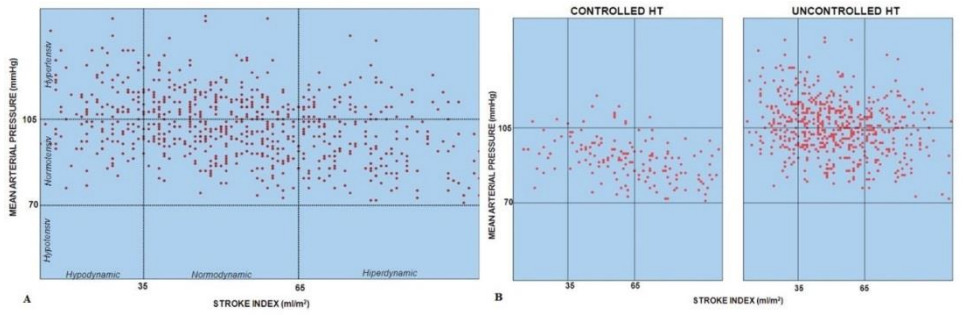

Figure 3.The hemodynamic map of the whole study sample (A), controlled and uncontrolled hypertensives (B) respectively.

Analysis of impedance cardiography recordings revealed 22 different HD profiles, 9 of them including hypervolemia. Only 6.2% of the screened subjects had a normal HD profile.

The prevalence of each of the altered hemodynamic modulators was as follows: hypervolemia 80.7%, hypovolemia 1.4%, vasoconstriction 26.3%, vasodilatation 25%, hyperinotropism 22.7%, hypoinotropism 33.5%.

The frequency of any alteration in HD modulators was significantly higher in uncontrolled hypertensives than in controlled ones (Table 2).

Table 2: Hemodynamic modulators and hemodynamic state of the study sample

	WG N = 771	**Uncontrolled HT N= 603**	**Controlled HT N = 168**	**P***
Volemia:				
• Hypovolemia	11 (1.4)	1 (0.6%)	10 (1.7)	<0.0001
• Normovelemia	138 (17.9%)	61 (36.3%)	77 (55.8%)	<0.0001
• Hypervolemia	622 (80.7%)	106 (63.1%)	516 (85.6%)	<0.0001
Vasoreactivity				
• Vasoconstriction	203 (26.3%)	32 (19%)	171 (28.4%)	<0.0001
• Normal	375 (48.6%)	71 (42.3%)	304 (81.1%)	<0.0001
• Vasodilatation	193 (25%)	65 (8.4%)	128 (21.2%)	<0.0001
Inotropism				
• Hipoinotropism	258 (33.5%)	41 (24.4%)	217 (36%)	<0.0001
• Normal	338 (43.8%)	62 (36.9%)	276 (45.8%)	<0.0001
• Hyperinotropism	175 (22.7%)	65 (38.7%)	110 (18.2%)	<0.0001
Hemodynamic state				
• Hipodynamic	137 (17.8%)	17 (10.1%)	120 (19.9%)	<0.0001
• Normal	399 (51.8%)	76 (45.2%)	323 (53.6%)	<0.0001
• Hyperdynamic	235 (30.5%)	75 (44.6%)	160 (26.5%)	<0,0001

*Values are present as absolute number (percent); WG: whole study group; HT: hypertension; N: total number of subjects; *chi square test.*

In the majority (93%) of Romanian hypertensives at least 1 altered HD modulator was found.

Regression analysis revealed a positive association between the number of altered HD modulators and the lack of BP control: 1 altered HD modulator: OR 2.57, 95%CI for OR (1.03-6.45), p = 0,044; 2 altered HD modulators: OR 2.89, 95%CI for OR (1.16-7.20), p = 0,022; 3 altered HD modulators: OR 1.67, 95%CI for OR (1.67-4.33), p = 0,027; 4 altered HD modulators: OR 2.54, 95%CI for OR (1.04-6.25), p = 0,042. The model has 80.2% power of correctly predicting lack of optimal BP control.

Mean estimated salt-intake in our study sample was 13.15±4.16mg/day NaCl, being significantly higher, on an average with 3,84mg/day higher in uncontrolled HT subjects than in controlled ones (Table 1).

Among hypervolemic hypertensive subjects, mean estimated salt-intake in our study sample was 13.26±4.03mg/day NaCl, also significantly higher among uncontrolled ones, on an average with 1.74mg/dayNaCl (uncontrolled hypervolemic HT: 13.55±4.09mg/dayNaCl vs. controlled hypervolemic HT: 11.81±3.41mg/dayNaCl; p <0,0001)

Among uncontrolled HT subjects, bivariate correlation analysis showed a strong direct correlation between estimated salt-intake and hypervolemic status (r_s^2 = 0.49; p = 0,005).

Although the most frequently used antihypertensive drugs were diuretics, angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers (BBs) (ACEIs: 45.3%, ARBs: 10.8%, diuretics: 46.8%, BBs: 39.6%. calcium-channel blockers: 18.7% and centrally active antihypertensive drugs: 2.9%; p <0.0001), only 41.4% of hypertensive patients with a vasoconstriction pattern were receiving vasodilatator drugs, only 20.5% of hypertensive patients with a hyperinotropism pattern were treated with beta-blockers, and only 1,4% of hypervolemic hypertensives were receiving diuretics (Figure 4).

Three hundred sixty-nine subjects, representing 47.3% of the study sample gave an affirmative answer to any question from the 4-item Morisky questioner, suggesting the presence of an adherence problem. As expected, among treated hypertensive subjects, adherence decreased as the number of antihypertensive drugs used for their treatment increased (1 drug: 54.5% vs. 2 drugs: 26,3% vs. 3 or more drugs: 12.4%; p = 0,035). There was also a decrease in adherence as the number of altered HD modulators increases (no altered modulators: 63.2% vs 1 altered modulator: 47.3% vs. 2 altered modulators: 24.5% vs. 3 or mode altered modulators: 11.5%; p = 0.025). Bivariate correlation analysis showed an indirect correlation between adherence to antihypertensive treatment and both number of drugs used (rS2 = 0.270; p = 0,035) and the number of altered hemodynamic modulators (rS2 = 0.348; p = 0,023).

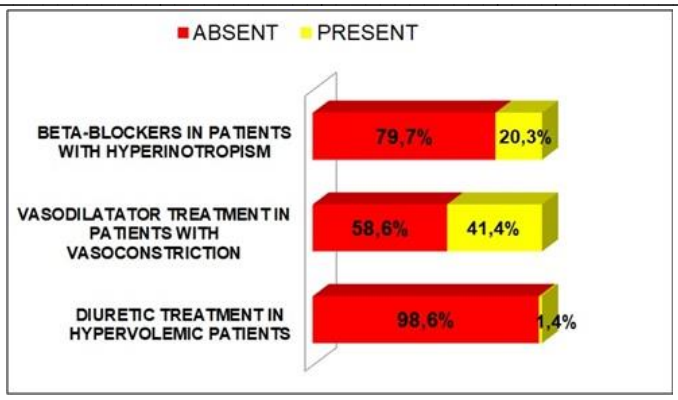

Figure 4. Antihypertensive treatment and hemodynamic imbalance

4. DISCUSSION

The importance of this study consists in the wealth of the data it provides regarding the hemodynamic profiling of a large hypertensive population (771 cases) from a national-representative survey conducted in a high cardiovascular risk country, Romania. Previous studies analysed only selected groups of hypertensive patients, such as those with resistant or uncontrolled HT. To the best of our knowledge, there is no data on a population level regarding the non-invasive hemodynamic characterisation of hypertensive patients.

According to the hemodynamic status and hemodynamic modulators (inotropism, vasoactivity, volemia) the present study reports similar results to a study conducted in 2013, in 9 European Centres of Excellence in Hypertension which aimed to monitor the hemodynamic profile (using also HOTMAN ® System) of 134 patients with uncontrolled hypertension treated by at least 2antihypertensive drugs. [15]Both studies demonstrate that hypertensive patients have a multitude of different HD profiles, which emphasizes the need of assessing their HD characteristics before choosing the appropriate antihypertensive drug for treatment.

Another significant finding of our study consists in the identification of the most frequent reason for suboptimal BP control in Romania, offering ground for future prevention strategies. Hypervolemia is the most frequent HD alteration in our Romanian hypertensive population, probably due to increased salt-intake [4] and/or inadequate use of diuretic treatment. This finding questions the indication in the 2013 ESH-ESC Guidelines for the Management of Hypertension, which states that antihypertensive therapy can be started with any of the classes of medication. At least in countries where dietary salt-intake are high such as Romania [4], the use of thiazide diuretics like in the former 2003 ESH-ESC Guidelines, may represent a better treatment option.

The current study also revealed that Romanian hypertensives have at least 1 altered HD modulator and identified a significantly higher number of different HD profiles in uncontrolled HT subjects compared to controlled ones (22 vs. 18), proving that lack of optimal BP control is associated with hemodynamic imbalance.

Another important reason for lack of optimal blood pressure control is non-adherence, aspect investigated in SEPHAR III survey by means of 4-item Morisky adherence questionnaire.

As previously reported in the main results of SEPHAR III survey [4] adherence to antihypertensive medication in Romania is low, almost half of the study sample being non-adherent to antihypertensive treatment, and the proportion of non-adherent subjects directly increasing by the number of antihypertensive drugs used in their treatment. More, our results reveal that lack of adherence to antihypertensive treated is also associated with HD imbalance.

Although optimal BP control was recorded in almost 30% of the study sample, a normal HD state was recorded in less than 10% of the sample, high lining the fact that a normal HD state is not equal to normal BP values. A normal HD state implies a simultaneous normal MAP and normo-dynamic stroke index (SI). The remaining 20% of the hypertensive subjects with BP <140/90mmHg, defining optimal BP control, still have abnormal HD profile (hyperdynamic or hipodynamic) and therefore this may lead to the development of adverse reactions to medical treatment leading to low treatment adherence. In this way we can explain the correlation observed in our study between the hemodynamic imbalance and low treatment adherence.

Although the use of diuretics, RAAS blockers and beta-blockers were used in the treatment of most of our hypertensive population, their proper use addressing the specific HD imbalance was scarcely employed. Therefore, being "blinded" to the HD profiles of our hypertensive patients, we may not offer the right drug to the right patient.

Currently, antihypertensive treatment in Romania, as it is world-wide, is unrelated to the hemodynamic profile. This may lead to hemodynamic imbalance, low adherence to antihypertensive treatment and lack of optimal BP control by choosing drugs that are unable to match the individual patient’s HD profile.

5. Future perspectives - could we do better?

By implementing an Integrated Hemodynamic Management that targets correction of all altered hemodynamic modulators in order to achieve simultaneously normal blood pressure and normal cardiac output, we can develop a novel additional approach to hypertension management. The treatment goal of the future may be: normalization of the hemodynamic profile and thus maximizing the effect of existing therapeutic strategies, individualizing antihypertensive therapy according to HD profile by choosing the best drug that fits the hemodynamic profile of the patient and help in improving BP control in hypertensive patients.

Future prospective studies on that antihypertensive drug treatment initiated or changed based on HD profile are needed to confirm our results: that in real life, impedance cardiography technique is of help to manage patients with HT.

6. Study limits

Since the data used for the analysis of this paper come from SEPHAR III survey database, its inherent limitations cannot be overcome and invites for cautious interpretation of our results.

First, since SEPHAR III was a large scale epidemiologic survey with more than 2000 screened subjects, the use of ambulatory blood pressure monitoring for a thorough diagnosis of HT and HT control could not be implemented.

Second, although the 4-item Morisky scale is an imperfect tool for evaluation of medication adherence compared to direct measurement of the drug or its metabolite concentration in blood or urine, MMAS-4 is the most widely used scale for research especially for assessing adherence to antihypertensive therapy and was chosen to be used in SEPHAR III since is easy and quickest to be administered, being suitable for large scale evaluations. [20-22].

Third, non-invasive HD evaluation by thoracic electrical bioimpedance has its inherent limitations such in the case of extreme obesity, severe COPD and high-ventricular rate AF subjects. To minimise these influences, we've excluded the data recorded from subjects presenting these conditions.

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DECLARATION OF INTEREST STATEMENT–The authors report no conflict of interest.

REFERENCES

[1] **Global status report on non-communicable diseases 2010**. Available from: http://www.who.int/nmh/publications/ncd_report_full_en.pdf;

[2] **High blood pressure. Global and Regional Overview**. Available from: http://www.searo.who.int/entity/world_health_day/leaflet_burden_hbp_whd2013.pdf;

[3] **Danaei G. et al.(2011),** ***National, Regional, and Global Trends in Systolic Blood Pressure since 1980: Systematic Analysis of Health Examination Surveys and Epidemiological Studies with 786 Country-years and 5•4 Million Participants***. The *Lancet*, 2011; 377(9765):568–577;

[4] **Dorobantu M., Tautu O., Dimulescu D. et al.(2018),** ***Perspectives on Hypertension's prevalence, Treatment and Control in a High Cardiovascular Risk East European Country****:* data from the SEPHAR III survey. J Hypertens. 2018 Mar;36(3):690-700;

[5]**Weber M., Schiffrin E., White W. et al.(2014), Clinical** ***Practice Guidelines for the Management of Hypertension in the Community a Statement by the American Society of Hypertension and International Society of Hypertension***. Journal of Hypertension. 2014; 32(1): 3-16;
[6]**Dorobantu M., Darabont R., Ghiorghe S. et al.(2014),** ***Hypertension Prevalence and Control in Romania at a Seven-year Interval.*** Comparison of SEPHAR I and II surveys. J. Hypertens. 2014;32(1):39-47;
[7]**Dorobantu M., Tautu O.F., Darabont R., Ghiorghe S., Badila E., Minca D. et al. (2015),** ***Objectives and Methodology of Romanian SEPHAR II Survey. Project for Comparing the Prevalence and Control of Cardiovascular Risk Factors in Two East-European Countries: Romania and Poland***. Archives of Medical Science. Arch Med Sci. 2015 Aug 12; 11(4): 715–723;
[8]**Wolf-Maier K., Cooper R.S., Banegas J.R., Giampaoli S., Hense H.W., Joffres M. et al.(2003),** ***Hypertension Prevalence and Blood Pressure Levels in 6 European Countries, Canada, and the United States***. JAMA 2003;289:2363–2369;
[9]**Wolf-Maier K., Cooper R.S., Kramer H., Banegas J.R., Giampaoli S., Joffres M.R. et al.(2004),** ***Hypertension Treatment and Control in Five European Countries, Canada, and the United States***. Hypertension 2004; 43:10–17;
[10]**Mancia G., Fagard R., Narkiewicz K., Redòn J., Zanchetti A., Böhm M. et al. (2013),** ***ESH/ESC Guidelines for the Management of Arterial Hypertension***; J. Hypertens. 2013; 31:1281–1357;
[11]**Sramek, B.** ***Hemodynamics and Hemodynamic Management***: Easy as 1,2,3. Available at: http://www.hemodynamicsociety.org/syshemo.html
[12]**Sramek, B.(2002),** ***Systemic Hemodynamics and Hemodynamic Management,*** 3rd Edition, (2002). 1-130;
[13]**Kaplan N.M. (1990),** ***Clinical Hypertension***, 5th. Edition, 1990:57;
[14]**Waeber B., Feihl F.(2007),** ***Antihypertensive Therapy According to the ESH/ESCG Guidelines***. Rev Med Suisse. 2007 Sept. 12;3(124):2003-4;
[15]**Viigimaa, M., Talvik, A., Wojciechowska, W., Kawecka-Jaszcz, K., Toft, I., Stergiou, G. S, Coca, A. (2013),** ***Identification of the Hemodynamic Modulators and Hemo¬dynamic Status in Uncontrolled Hypertensive Patients***. Blood Pressure, 22(6), 362–70;
[16]**Ferrario C.M., Flack J.M., Strobeck J.E., Smits G., Peters C.(2010),** ***Individualizing Hypertension Treatment with Impedance Cardiography: A Meta-analysis of Published Trials***. Ther. Adv. Cardiovasc. Dis. 2010;4(1):5-16;
[17]**Elmula F, Hoffmann P., Larstorp A.C., Fossum E., Brekke M., Kjeldsen S.E. et al.(2014),** ***Adjusted Drug Treatment is Superior to Renal Sympathetic Denervation in Patients with True Treatment-resistant Hypertension***. Hypertension. 2014 May;63(5):991-9;
[18]**Albert N.M.(206),** ***Bioimpedance Cardiography Measurements of Cardiac Output and other Cardiovascular Parameters***. Crit. Care Nurs. Clin. North Am. 2006;18(2):195-202;

[19]**Dorobantu M., Darabont R., Dimulescu D. et al.(2016),** ***New National Epidemiological Survey for the Assessment of Trend in Hypertension's Prevalence, Treatment and Control among the Adult Population of Romania***: SEPHAR III - design and methodology. J Hypertens Res (2016) 2(4):143–152;
[20]**Tan X., Patel I., Chang J., et al.(2014),** ***Review of the four item Morisky Medication Adherence Scale (MMAS-4) and eight item Morisky Medication Adherence Scale (MMAS-8).*** Inov Pharm. 2014;5(3): Article 165;
[21]**Mary G.G.** ***Understanding and Improving Medical Adherence***. In Hypertension: A Companion to Braunwald's Heart Disease, Third Edition. Bakris G.L. and Sorrentino M Editors. *Elsevier*. 453-458;
[22]**W.Y. Lam, P. Fresco (2015),** ***Medication Adherence Measures: An Overview.*** Biomed Res Int. 2015; 2015: 217047;
[23]**Kawasaki T., Itoh K., Uezono K., Sasaki H.(1993),** ***A Simple Method for Estimating 24 H Urinary Sodium and Potassium Excretion from Second Morning Voiding Urine Specimen in Adults***. ClinExpPharmacol Physiol. 1993 Jan;20(1):7-14.