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A “patient-tailored” treatment of hypertension with use of impedance cardiography: A randomized, prospective and controlled trial

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG **Paweł Krześciński**
ABCDEF **Grzegorz Gerard Gielerek**
ABDE **Jarosław Józef Kowal**

Department of Cardiology and Internal Diseases, Military Institute of Medicine, Warsaw, Poland

Corresponding Author: Paweł Krześciński, e-mail: pkrzescinski@wim.mil.pl
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Background: Arterial hypertension might be caused by hemodynamic disturbances such as fluid retention, increased vascular resistance, and hyperdynamic function of the heart. The aim of this study was to estimate the effectiveness of antihypertensive therapy based on hemodynamic assessment by impedance cardiography in a randomized, prospective, controlled trial.





Material/Methods: This study involved 128 patients (average age: 42.9±11.1 years) with arterial hypertension, randomized into groups: (1) empiric, and (2) hemodynamic, in which treatment choice considered impedance cardiography results. Evaluation of treatment effects was performed after 12 weeks and included office blood pressure measurement and ambulatory blood pressure monitoring.

Results: All final blood pressure values were lower in the hemodynamic group, significantly for office systolic blood pressure (empiric vs. hemodynamic: 136.1 vs. 131.6 mmHg; p=0.036) and diastolic blood pressure (87.0 vs. 83.7 mmHg; p=0.013), as well as night-time systolic blood pressure (121.3 vs. 117.2 mmHg; p=0.023) and diastolic blood pressure (71.9 vs. 68.4 mmHg; p=0.007). Therapy based on impedance cardiography significantly increased the reduction in office systolic blood pressure (11.0 vs. 17.3 mmHg; p=0.008) and diastolic blood pressure (7.7 vs. 12.2 mmHg; p=0.0008); as well as 24-h mean systolic blood pressure (9.8 vs. 14.2 mmHg; p=0.026), daytime systolic blood pressure (10.5 vs. 14.8 mmHg; p=0.040), and night-time systolic blood pressure (7.7 vs. 12.2 mmHg; p=0.032).

Conclusions: Antihypertensive treatment based on impedance cardiography can significantly increase blood pressure reduction in hypertensive patients.

Key words: **hypertension • blood pressure • impedance cardiography • cardiovascular diseases • antihypertensive agents • hemodynamics**

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Background

Arterial hypertension (AH) is an important clinical, social and economic problem. It is estimated to affect 1/4 of world's population [1]. AH is the main risk factor for ischaemic heart disease, heart failure, kidney failure and stroke. In the pathogenesis of hypertension, increased arterial tension is a result of complex mechanisms, and might be caused by fluid retention, increased vascular resistance, hyperdynamic function of the heart, etc. Current guidelines stress that antihypertensive therapy choice should be based on individual patient assessment [2,3].

Impedance cardiography (ICG) is an easy technique for noninvasive hemodynamic monitoring of parameters that accurately characterize participation of these mechanisms in development of hypertension. It allows for assessment of cardiac index (CI), heart rate (HR), thoracic fluid content (TFC), and systemic vascular resistance index (SVRI) [4]. Clinical studies carried out so far demonstrated the effectiveness of ICG in individualization of antihypertensive treatment. According to Taler et al. [5], ICG provides a better choice of medications and doses in terms of a patient's individual hemodynamic status. Smith et al. [6] also suggest that the use of ICG in hypertensive patients significantly improves treatment effectiveness and allows for monitoring therapy effects. However, there are no clear indications regarding therapy based on hemodynamic measurements and their criteria values, which significantly limits possibilities of using ICG in clinical practice.

The aim of this study was to estimate the effectiveness of a treatment algorithm based on hemodynamic parameters assessed by ICG in therapy of mild and moderate AH in a randomized, prospective, controlled trial.

Material and Methods

Study population

The study involved patients with at least 3-month history of mild or moderate AH defined according to European Society of Cardiology guidelines [2]. The study was carried out in the Department of Cardiology and Internal Diseases, Military Institute of Medicine from March 2008 to June 2009.

Study inclusion criteria comprised: (1) not treated AH: increased blood pressure for at least 3 months and, (2) AH improperly controlled with 1 or 2 antihypertensive medicines. Exclusion criteria comprised: (1) confirmed secondary AH, (2) improperly controlled AH with 3 or more medicines, (3) heart failure, (4) cardiomyopathy, (5) significant heart rhythm disorders, (6) significant valvular disease, (7) kidney failure, (8)

chronic obstructive pulmonary disease, (9) diabetes, (10) polyneuropathy, (11) peripheral vascular diseases, and (12) age <18 years and >65 years.

The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the Ethics Committee, Military Institute of Medicine (no 3/WIM/2008). Written informed consent was obtained from all patients prior to their inclusion into the study. The study was registered at www.nauka-polska.pl (ID 227062).

Study design

The study was randomized (1:1), prospective, and simultaneously controlled by conventional treatment. Initial clinical evaluation was performed on the first visit. Patients who had been taking medicines before the study were advised to stop, and to take captopril sublingually in case of increased blood pressure.

On the second visit (after 2 weeks), all patients underwent the following examinations: interview and physical examination with office blood pressure measurement (OBPM), 24-h ambulatory blood pressure monitoring, ICG, electrocardiogram, echocardiography, and laboratory tests (ionogram, creatinine, fasting glucose, lipidogram).

After those examinations, the patients were divided into 2 groups according to previous randomization (with the use of RandomBots Medusa 2.0.2 software): (1) empiric group (GE), in which treatment choice was based on clinical data; and (2) hemodynamic group (HD), in which treatment choice was based on clinical data considering hemodynamic parameters established with ICG (Figure 1). Treatment choice in both groups was made by independent researchers. Evaluation of treatment effects was performed by the researcher, blinded to assigned treatment on the third visit after 12 weeks, while carrying out control examinations, including office blood pressure, 24-h ambulatory blood pressure monitoring, and ICG.

Differences between the groups within blood pressure absolute values, blood pressure reduction and obtained blood pressure control after 12-week treatment were considered as final points (per protocol analysis).

Clinical examination

Clinical examination was performed during all the visits, with special consideration of history of cardiovascular risk factors and symptoms indicating secondary cause of AH, as well as organ damage. OBPM (Omron M4 Plus, Japan) was performed by technique compliant with European Society of Cardiology guidelines [2].

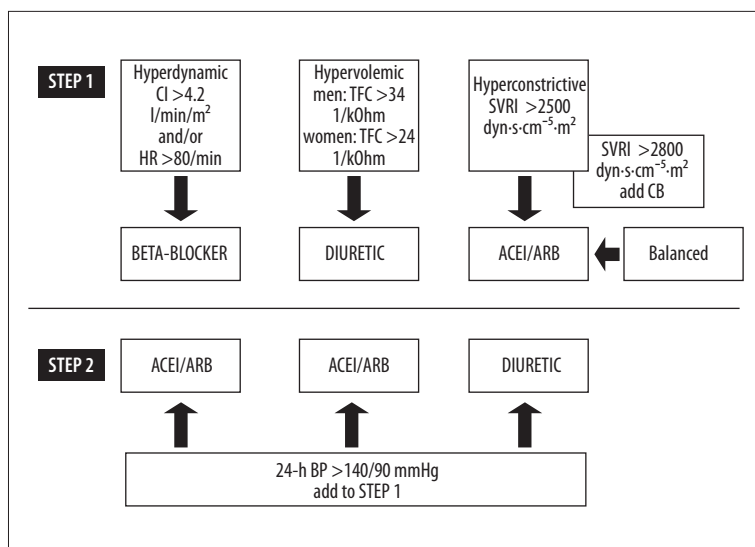


Figure 1. Treatment algorithm based of particular hemodynamic parameters. ACEI – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, BP – blood pressure, CB – calcium blocker, CI – cardiac index, HR – heart rate, SVRI – systemic vascular resistance index, TFC – thoracic fluid content.

Ambulatory blood pressure monitoring (ABPM)

All the patients included in the study underwent ABPM (Spacelabs 90207, Spacelabs, Medical Inc, Redmond, USA). Time from 6 a.m. to 10 p.m. was considered the daily activity period (daytime), with automatic blood pressure measurement in 10-minute intervals. During night rest (night-time: 10 p.m. – 6 a.m.), the measurement was performed every 30 minutes. Test results were interpreted according to European Society of Cardiology guidelines [2].

Impedance cardiography (ICG)

Measurement of hemodynamic parameters with ICG method was performed during a 10-minute examination at rest (Niccomo, Medis, Germany) in horizontal position in morning hours (7.30–8.30). Blood pressure measurement was performed automatically every 2 minutes with an arm cuff. The other hemodynamic parameters were measured by the beat-to-beat method. The values of TFC, CI, SVRI, and HR from the 5th minute of the examination were taken into account in the treatment algorithm.

Cut-off values of SVRI, CI, HR, and TFC (from the 5th minute of the ICG examination) were as follows: (1) hyperconstrictive profile: in the case of SVRI >2500 dyn·s·cm⁻⁵·m², (2) hyperdynamic profile: as CI >4.2 l/min/m² and/or HR >80/min, (3) hypovolemic profile: as TFC >34 1/kOhm for men and >24 1/kOhm for women, and (4) balanced profile: as hemodynamic parameters below established threshold values.

The groups requiring combined therapy with regard to significantly increased blood pressure (mean blood pressure in the 24-h measurement period >140/90 mmHg) were also distinguished.

Echocardiography

To exclude any important heart abnormalities, echocardiography with the use of Vivid 7 apparatus (GE-Healthcare, the USA) was performed in the morning hours (7.30–8.30) according to current Standards of Echocardiography Society of Polish Cardiac Society [7].

Treatment

Non-pharmacological treatment was administered according to current guidelines [2]. Pharmacotherapy included drugs whose effectiveness in hypertension treatment had been confirmed in many clinical studies [8–14]: lisinopril (ACEI, angiotensin-converting enzyme inhibitor), telmisartan (ARB, angiotensin receptor blocker), hydrochlorothiazide (thiazide diuretic), metoprolol (BB, beta-blocker), and amlodipine (CB, calcium blocker).

In the GE group the treatment was based on current guidelines. In monotherapy, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was preferred. In polytherapy, the second drug was: (1) thiazide diuretic in older patients, with isolated systolic hypertension, with features of fluid retention and intolerance of calcium blocker in the past; (2) CB in patients with metabolic syndrome; and (3) BB in younger patients and the occurrence of symptoms of increase sympathetic drive (e.g., tachycardia).

Treatment algorithm in HD group (Figure 1) was arbitrarily determined. Absolute CI and SVRI values were established based on previous studies [5,6,15,16]. TFC for both men and women were defined based on patients' characteristics from clinical trials [5,6], referring to the computational algorithm (sex-dependant) used in a Niccomo device. Taking into account the fact that increased HR had been reported to be unfavorable

for prognosis [17–20], HR >80/min at rest (from the 5th minute of the ICG examination) was considered as an additional indication to use beta-blocker.

In STEP 1, when the patient's hemodynamic profile was hyperdynamic – BB was recommended; when hypervolemic – thiazide diuretic; and when hyperconstrictive – ACEI or ARB (if SVRI was >2800 dyn·s·cm⁻⁵·m² – ACEI/ARB with CB was recommended). In cases of complex hemodynamic disturbances, the combined therapy was used. STEP 2 was reserved for the patients with 24-h mean blood pressure >140/90 mmHg – they were assumed to demand polytherapy and when ICG suggested only one hemodynamic disturbance (indication for the first drug) the second drug was added in combination as in Figure 1.

Statistical analysis

On the basis of the results of Smith et al. [6], the sample size for minimum change in office SBP reduction of 6 mmHg after 12 weeks of follow-up was calculated as 45 patients per treatment group (HD vs. GE, α -error 5%, statistical power 80%).

Statistical analysis of the obtained results was performed using Statistica 7.0 software (StatSoft Inc., USA). Normality of data distribution was checked by the Shapiro-Wilk test. All results are expressed as average values \pm SD for continuous variables and number of patients, as well as percentages for categorical variables. The groups and treatment effects were compared by the use of Student's *t* tests for normally distributed data, and non-parametric tests (Mann Whitney U test, χ^2 test/Fisher's exact test) for other than normally distributed data. $P < 0.05$ was considered statistically significant.

Results

Baseline clinical data

The study involved a group of 128 consecutive patients (91 men), average age 42.9 \pm 11.1 years (range: 19 to 65 years), with baseline characteristics presented in Table 1. The hemodynamic profiles in the study group were differentiated: increased SVRI was observed in 43.8% of patients, 25.8% of them were hypervolemic and 25.8% had hyperdynamic heart function. Almost 1/4 (22.0%) were characterized by balanced hemodynamic profile.

Treatment effects

Figure 2 shows the protocol flowchart for a mean time of observation of 91.4 \pm 10.0 days. Fourteen patients were excluded from the final analysis because of meeting the exclusion criteria mentioned above.

Most commonly administered drugs in both groups were angiotensin-converting enzyme inhibitor (GE vs. HD: 54.6% vs. 47.5%, $p=0.449$), and angiotensin receptor blocker (34.6% vs. 37.3%, $p=0.760$). Polytherapy was less frequently administered in the GE group than in the HD group (48.3% vs. 66.1%, $p=0.042$). It was connected with more frequent use of beta-blocker (20.0% vs. 33.9%, $p=0.096$) and calcium blocker (9.1% vs. 23.7%, $p=0.036$) in the HD group, mostly in combined therapy. The use of diuretic was comparable (29.1% vs. 32.2%, $p=0.719$).

All final blood pressure values were lower in the HD group, significantly so for office blood pressure and night-time blood pressure. Analysis of change in average blood pressure values showed significantly greater blood pressure decrease in the HD group, especially in office blood pressure and average SBP values in ABPM (Table 2, Figure 3). In HD group a higher percentage of patients with proper blood pressure control in office blood pressure and ABPM was observed. However, according to statistical assessment, significant differences occurred only for night-time DBP (such trend was also observed for other BP variables – Table 3).

Discussion

The discussion of antihypertensive treatment has lasted for many years, yet still no clear management algorithm has been found for antihypertensive pharmacotherapy. Therefore, according to the guidelines of world cardiac societies, management of hypertensive patients should focus on detailed diagnostics that allow individualization of treatment and evaluation of risk factors [2,3].

ICG is becoming an increasingly used tool for non-invasive hemodynamic monitoring. Its usefulness and accuracy in evaluation of the cardiovascular system in hypertensive patients results from a possibility of simultaneous evaluation of many hemodynamic parameters. Current guidelines, other researchers' observations, and the authors' own experiences in using ICG in antihypertensive treatment allowed for compilation of algorithm of antihypertensive treatment based on particular hemodynamic parameters. The methods of evaluating treatment effects allowed for objective assessment of the value of the suggested therapy.

Characteristics of patient population

ICG assessment revealed significant variety in patients' hemodynamic profiles. Signs of vasoconstriction were most common, while hypervolemia and hyperdynamic function of cardiac muscle were present in every fourth patient. The study population comprised young and middle-aged patients, which

Table 1. Basic characteristics.

	GE (n=63)	HD (n=65)	p	Study group (n=128)
Men, n (%)	47 (74.6)	44 (67.7)	0.389	91 (71.1)
Age (years), mean \pm SD	42.6 \pm 11.2	43.2 \pm 11.0	0.869	42.9 \pm 11.1
BMI (kg/m ²), mean \pm SD	28.5 \pm 4.7	28.6 \pm 3.9	0.744	28.6 \pm 4.3
SBP (mmHg), mean \pm SD	147.9 \pm 9.7	148.4 \pm 13.6	0.858	148.2 \pm 11.8
DBP (mmHg), mean \pm SD	95.4 \pm 8.4	95.7 \pm 8.2	0.324	95.6 \pm 8.3
Nicotinism				
Presently, n (%)	16 (25.4)	14 (21.5)	0.606	30 (23.4)
In the past, n (%)	18 (28.6)	20 (30.8)	0.786	38 (29.7)
Treatment before recruitment				
Yes, n (%)	19 (30.2)	15 (23.1)	0.364	34 (26.6)
Family history				
AH, n (%)	29 (46.0)	35 (53.9)	0.376	64 (50.0)
Symptoms				
Headaches, n (%)	27 (42.9)	34 (52.3)	0.285	61 (47.7)
Malaise, n (%)	20 (31.8)	20 (30.8)	0.905	40 (31.3)
Dizziness, n (%)	7 (11.1)	2 (3.1)	0.076	9 (7.0)
Vision disorders, n (%)	4 (6.4)	4 (6.2)	0.964	8 (6.3)
Asymptomatic, n (%)	25 (39.7)	23 (35.4)	0.616	48 (37.5)
Concomitant diseases				
Dyslipidemia	43 (68.3)	47 (72.3)	0.616	90 (70.3)
Metabolic syndrome	32 (50.8)	40 (61.5)	0.221	72 (56.3)

AH – arterial hypertension; BMI – body mass index; DBP – diastolic blood pressure; IHD – ischaemic heart disease; SBP – systolic blood pressure; SD – standard deviation.

suggests the need for caution in extrapolation of the observations to other age groups. According to other researchers [5,6,21,22], the percentage of disorders connected with hyperdynamic function of cardiac muscle among older people would be significantly lower, while the number of patients with signs of hyperconstriction and hypervolemia would rise.

Comparison of treatment effects

The effects of antihypertensive treatment were very good in both groups – almost all average blood pressure values were within suggested norms. At the same time, it was observed that use of hemodynamic measurements increased effectiveness of antihypertensive therapy. Analysis of changes in blood pressure values revealed more strongly expressed antihypertensive effect in the HD group, both in office blood pressure and ABPM. Office blood pressure and ABPM pressure control

were higher in the HD group. Although the differences were statistically significant only for night-time DBP, the 15% increase in percentage of patients with complete blood pressure control in ABPM seems to be clinically important.

When comparing these results to other researcher's observations, works by Smith et al. [6] and Taler et al. [5] should be considered. In the CONTROL study [6], patients with no significant accompanying diseases, and with average blood pressure about 155/93 mmHg, underwent a 3-month therapy in which the HD group was modified based on comparing monthly ICG results (BioZ ICG Monitor, CardioDynamics). The authors considered normalization of CI (within 2.5–4.2 l/min/m²) and SVRI (1680–2580 dyn·s·cm⁻⁵·m²) to be a substitute final product. Therapy based on hemodynamic evaluation was connected with significantly better blood pressure control, including a considerable decrease of average SBP and DBP values. The HD

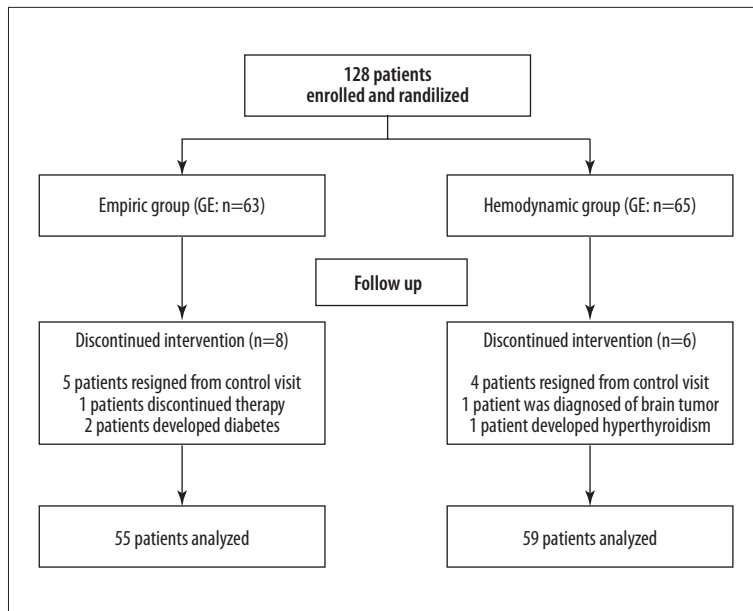


Figure 2. The protocol flowchart.

Table 2. Treatment effect within BP and hemodynamic parameters.

	GE (n=55)	HD (n=59)	P
OBPM, mean ±SD			
SBP (mmHg), baseline	147.1±9.5	148.9±13.8	0.428
SBP (mmHg), after 12 weeks	136.1±12.0	131.6±11.4	0.036
DBP (mmHg), baseline	94.8±7.8	95.9±8.4	0.422
DBP (mmHg), after 12 weeks	87.0±7.1	83.7±6.7	0.013
ABPM, mean ±SD			
24-h mean SBP (mmHg), baseline	140.0±10.1	141.8±10.4	0.302
24-h mean SBP (mmHg), after 12 weeks	130.2±9.4	127.7±8.6	0.135
24-h mean DBP (mmHg), baseline	88.2±8.2	88.1±8.2	0.967
24-h mean DBP (mmHg), after 12 weeks	79.7±7.8	78.0±6.1	0.186
Daytime SBP (mmHg), baseline	144.3±10.3	147.0±10.4	0.130
Daytime SBP (mmHg), after 12 weeks	133.8±10.1	132.2±8.9	0.368
Daytime DBP (mmHg), baseline	91.7±8.6	92.3±8.6	0.704
Daytime DBP (mmHg), after 12 weeks	82.6±8.6	81.6±6.1	0.408
Night-time SBP (mmHg), baseline	129.0±10.9	129.4±12.2	0.871
Night-time SBP (mmHg), after 12 weeks	121.3±9.5	117.2±9.8	0.023
Night-time DBP (mmHg), baseline	78.8±8.9	77.9±8.8	0.565
Night-time DBP (mmHg), after 12 weeks	71.9±7.2	68.4±6.4	0.007

ABPM – ambulatory blood pressure monitoring; DBP – diastolic blood pressure; OBPM – office blood pressure measurement; SBP – systolic blood pressure; SD – standard deviation.

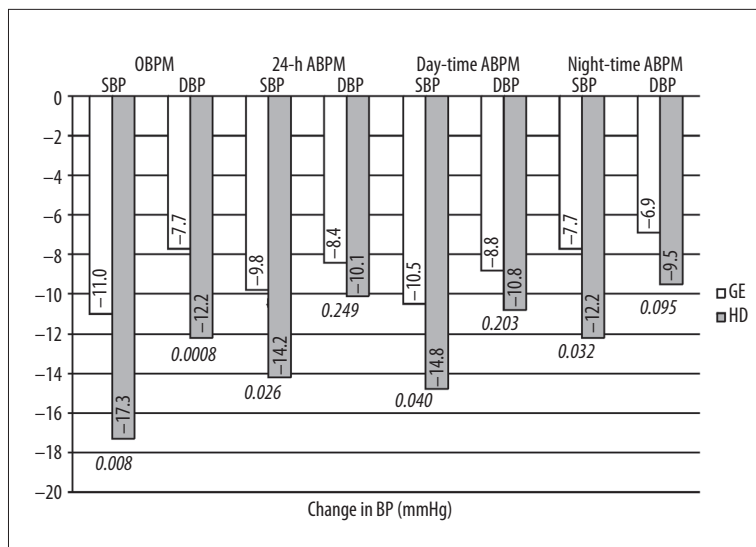


Figure 3. Treatment effect within BP change (p value in italic).

Table 3. Treatment effect within BP control.

	GE (n=55)	HD (n=59)	P
OBPM < 140/90 mmHg, n (%)	25 (45.5)	36 (61.0)	0.096
ABPM*, n (%)	14 (25.4)	23 (40.0)	0.123
24-h mean SBP (mmHg), n (%)	29 (52.7)	40 (67.8)	0.100
24-h mean DBP (mmHg), n (%)	30 (54.6)	42 (71.2)	0.066
Daytime SBP (mmHg), n (%)	30 (54.6)	39 (66.1)	0.207
Daytime DBP (mmHg), n (%)	32 (58.2)	43 (72.9)	0.098
Night-time SBP (mmHg), n (%)	26 (47.3)	38 (64.4)	0.065
Night-time DBP (mmHg), n (%)	24 (43.6)	38 (64.4)	0.026

* 24-h mean BP <130/80 mmHg and daytime BP <135/85 mmHg and night-time BP <120/70 mmHg. ABPM – ambulatory blood pressure monitoring; DBP – diastolic blood pressure; OBPM – office blood pressure measurement; SBP – systolic blood pressure.

group had a higher percentage of subjects with blood pressure < 140/90 mmHg (77% vs. 57%; p<0.001), which is considered as the main final point. Good treatment effects in the HD group were more clearly expressed in this study, but its methods included 2 additional visits after the first and second month of therapy. Undoubtedly, it had a significant impact on treatment effects, as the therapy in the HD group was significantly modified during 3-months follow-up (frequency of withdrawals of initially chosen drug 0.8/treatment cycle, frequency of introducing a new drug 1.1/treatment cycle).

It is slightly more difficult to compare the obtained results to the work by Taler et al. [5], performed on a group of patients with resistant AH. Considerably higher initial blood pressure values (average 171/89 mmHg), older population (average age of 66 years), accompanying disorders (organ damage connected with AH – 47%, type 2 diabetes – 33%), and treatment with at least 2 drugs, suggest the need for caution in comparing these

populations. During 3 months, the treatment was modified in the HD group almost 5 times. For justified reasons (resistant hypertension), the obtained average blood pressure values in office blood pressure were higher than in the other studies, but the antihypertensive effect was also more clearly expressed in the HD group within average blood pressure values (GE vs. HD: 147/79±2/1 vs. 139/72±1/1 mmHg; p<0.01) and control of blood pressure <140/90 mmHg (33% vs. 56%; p<0.05).

The considerable improvement in antihypertensive treatment effect in the HD group might be of great importance in terms of prognosis. According to Williams' metaanalysis of clinical studies [23], a decrease in blood pressure by 4/3 mmHg is connected with decrease in risk of stroke (by 23%), coronary disease (15%), and overall mortality (14%). In young hypertensive patients, permanent treatment optimization should be related to significant improvement within primary prevention of cardiovascular disorders.

Administered treatment

HD patients were more frequently treated with more than 1 medication. However, significant differences applied to calcium blocker only used in polytherapy with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. It should be noticed that the most common polytherapy choice in the GE group was treatment with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and thiazide diuretic, which resulted from clinical experience and knowledge based on results of high quality clinical studies and previous guidelines [24–26]. In the HD group, the combination of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and calcium blocker was used with similar frequency, which agrees with current opinions in antihypertensive therapy formed in the ACCOMPLISH study [8]. The observed therapy trend in favour of vasodilators is similar to the CONTROL study, where drugs reducing SVRI were more frequently used in the HD group than in the GE group (92.8% vs. 80.0%) [6].

Observations of differences with greater frequency of administering polytherapy and number of used antihypertensive drugs require further comment. The detailed management algorithm in the HD group significantly limited subjectivity of the treatment choice. Concurrently, the treatment choice in the GE group was made by an experienced researcher and was based on his clinical experience and current guidelines. The therapeutic aim in both groups was to obtain proper blood pressure control,

with simultaneous caution concerning overly aggressive blood pressure decrease in a short period time. Importantly, administration of a slightly greater amount of drugs (17.8%) resulted in improvement of blood pressure reduction by nearly 50% compared to the GE group, which proves the accuracy of the chosen antihypertensive therapy.

Study limitations

The obtained results should be applied with caution in women and in patients with significant chronic diseases (both were minorities in this study). The impossibility of blinding the physician choosing the therapy in the HD group made a potential bias. However, we tried to limit it by designing an algorithm based on criteria values and blinded evaluation of the treatment effect. Assessment of the long-term effect of therapy based on ICG would be also of significant value.

Conclusions

Impedance cardiography is a useful and easy method for evaluating patients with mild and moderate AH, which provides clinically important complementary data. Use of an antihypertensive treatment algorithm based on criteria values of particular hemodynamic parameters can significantly increase blood pressure reduction in hypertensive patients.

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