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Evaluation of resistant hypertension in primary care settings

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Abstract

The objectives of the study were to evaluate the prevalence of resistant hypertension (HT) in primary care settings, its characteristics, differential diagnosis and therapy. During the period of 2010-2014 a number of 4681 hypertension patients were evaluated at 17 family medicine offices in Timiş county, Romania. The database included demographical and clinical variables as office blood pressure (OBP) measurements, ABPM, cardiovascular risk factors, target organ damage, cardiovascular events and therapy. A number of 673 patients (14.84%) did not reach the target OBP < 140/90 mmHg. ABPM demonstrated in 439 patients (65.23%) values ≥135/85 mmHg and normal ABPM data in 34.76%, confirming in the latter group a "white-coat effect". In the patient group with abnormal ABPM, 76.53% were evaluated by specialists and diagnosed with true resistant hypertension, as 17.08% presented pseudo-resistant and 6.37% secondary hypertension. Lifestyle factors implicated in resistant hypertension were obesity (58.03%), a sedentary lifestyle (55.95%), high salt intake (27.08%) and excessive alcohol consumption (11.9%). Compared with controlled hypertension, resistant hypertension patients had more often target organ damage (28.92% *versus* 17.13%) and cardiovascular diseases (22.87% *versus* 16.8%). Medication in resistant hypertension consisted of renin-angiotensin system blockers (79.6%), calcium channel blockers (54.6%), diuretics (100%), beta-blockers (41.9%) and other anti-hypertension drugs (47.5%).
Prevalence of true resistant hypertension was 7.17%. It was associated with a longer duration of hypertension, older age, higher blood pressure levels, obesity, diabetes mellitus, metabolic syndrome, multiple risk factors, target organ damage and cardiovascular diseases.

Keywords: Resistant hypertension-characteristics-differential diagnosis-primary care.

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Introduction

A situation often met in family medicine practice is that of hypertensive patients with BP values over the targets, though treated with multiple drugs.

Resistant hypertension is considered present in patients treated with at least 3 antihypertensive agents, including a diuretic, at optimal doses or maximal tolerated, with office blood pressures that exceed the target values of 140 and/or 90 mmHg. ABPM is necessary in this situation, as it permit the separation of patients with elevated OBP and elevated ABPM form those with isolated office resistant hypertension or "white-coat effect", who have elevated OBP, but normal ABPM [1]. The NICE Guidelines suggest that the diagnosis of resistant hypertension can be confirmed only after the documentation of abnormal ABPM data (mean day blood pressure ≥135/85 mmHg). Before considering a patient with abnormal OBP and ABPM as having true resistant hypertension, pseudo-resistant hypertension (false resistant HT) and secondary hypertension must be excluded [2].

The objectives of the study were to establish the prevalence of resistant hypertension in primary care settings, to evaluate the characteristics in comparison with controlled hypertension and to establish the differential diagnosis and therapy.

Material and methods

A number of 4681 hypertensive patients from 17 family medicine offices in Timiş County, Romania, were studied during 2010–2014. The database of the patients included demographic information, OBP measurements, 24-h ABPM, cardiovascular risk factors (plasma glucose levels, cholesterolemia, creatinine, microalbuminuria, obesity, metabolic syndrome, diabetes mellitus), target organ damage, cardiovascular and renal events and therapy.

All the family doctors insolved in the study were instructed to use the same methodology regarding blood pressure measurement and patient evaluation. Office blood pressure measurement was calculated as the average of the second and third measurement made during the morning at 3745 (80%) of patients and during the afternoon at 20%. The BP measurements were done with validated semiautomatic Omron sphygmomanometers. Four ABPM, BTL-08 ABPM devices were used, being programmed with 4 measurements /hour during daytime and 2 measurements /hour during night-time. The patients were advised to perform their usual activities and to have the upper arm extended during the cuff inflation. ABPM was accepted when over 80% of the measurements were valid [1].

The family doctors and nurses were instructed regarding correct BP measurements, investigation and management of the hypertensive patient´s lifestyle and therapy by the COMBAT courses of the Romanian Society of Hypertension.

Statistical analysis

Data were presented as frequencies and percentages for qualitative variables and as mean ± SD for quantitative variables. Differences between groups of variables were assessed with the Pearson χ^2 for qualitative variables and the Student t test for quantitative data. The independent variables with $p < 0.05$ were considered as having statistical significance. All the statistical analyses were performed using the software Stata 9.2.

Results

From the total number of 4681 evaluated hypertensive patients, after three months of treatment, time during which the BP of the patients and their compliance to treatment were monthly monitored, 695 cases (14.85%) did not reach the target OBP of <140/90 mmHg, being on treatment with 3 or more agents, one of which was a diuretic. They all underwent afterwards an ABPM. Due to of incomplete ABPM data, 22 hypertension patients were excluded, finally 673 patients being analysed.

ABPM documented normal daytime mean BP values (≤ 135/85 mmHg) in 234 (34.77%) patients, classified as having idiopathic office resistant hypertension or a "white-coat effect". The remaining 439 (65.23%) cases with abnormal ABPM followed investigation in diagnostic centres. In these, true resistant hypertension was diagnosed in 336 patients (76.53%), pseudo-resistant hypertension in 75 (17.08%) and secondary hypertension in 28 cases (6.37%) as shown in Figure 1.

The evaluation of lifestyle factors that had an important contribution to the development of resistant hypertension is presented in Figure 3.

The causes of pseudo-resistant hypertension were non-adherence to treatment (50.66%), suboptimal therapeutic drug regimens (37.33%), drugs that increase BP (6.66%) and other different causes (5.33%), as shown in Figure 2.

To analyse the characteristics of resistant hypertension we made a comparison of 336 patients with resistant hypertension with a group of 695 controlled hypertension patients (Table 1).

Compared with controlled hypertension, resistant hypertension patients had a longer duration of hypertension, an older age, especially over 60 years, a greater prevalence of diabetes mellitus, obesity, smoking, target organ damage and cardiovascular diseases.

Office BP values and ABPM data had statistical higher values in resistant hypertension compared with controlled hypertension as seen in Figure 4.

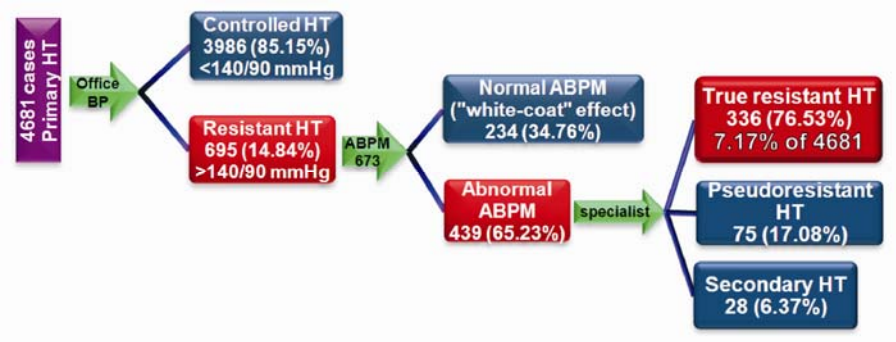

Figure 1. Design of the study.

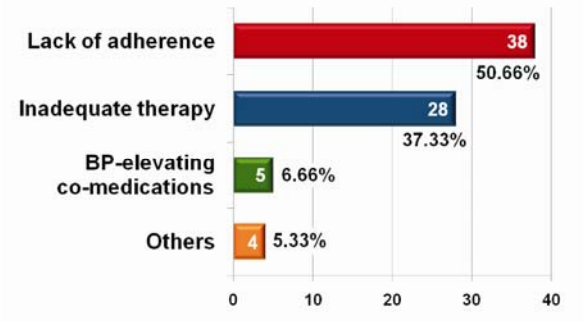

Figure 2. Etiology of pseudo-resistant hypertension.

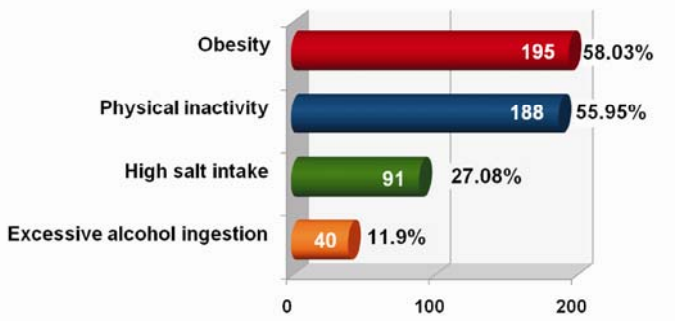

Figure 3. Lifestyle factors associated with resistant hypertension.

Table 1. Characteristics of patients with resistant and controlled hypertension

Characteristics	Resistant HT Nr = 336 cases	Controlled HT Nr = 695 cases	p
Age (years)	65.4 ± 11.4	60 ±11.6	<0.05
Age >60 years	68.45% (230 cases)	54.1% (376 cases)	<0.001
Male gender	52.67% (177 cases)	51.07% (355 cases)	NS
Smoking	19.04% (64 cases)	14.82% (103 cases)	<0.05
Dyslipidaemia	35.11% (118 cases)	33.52% (233 cases)	NS
BMI >30 kg/m^2	58.03% (195 cases)	34.96% (243 cases)	<0.001
Diabetes	31.84% (107 cases)	26.61% (185 cases)	<0.05
Duration of hypertension (years)	15 ± 8.9	12.1 ±8.1	<0.05
Target organ damage	28.86% (97 cases)	17.12% (119 cases)	<0.05
Cardiovascular diseases	22.91% (77 cases)	16.83% (117 cases)	<0.05

The analysis of the circadian BP patterns showed differences between true resistant hypertension and controlled hypertension, with a higher proportion of nondippers (65.47% *versus* 60.89%) in true RHT, based on either systolic or diastolic BP (p<0.001).

In resistant hypertension, compared with controlled hypertension, target organ damage and cardiovascular diseases were more fervent (Figure 5).

The evaluation by specialists in diagnostic centres confirmed in 6.37% cases (with abnormal ABPM data) a secondary hypertension. The principal causes of secondary hypertension were sleep apnoea, renal artery stenosis, primary hyperaldosteronism and diseases of the renal parenchyma (Figure 6).

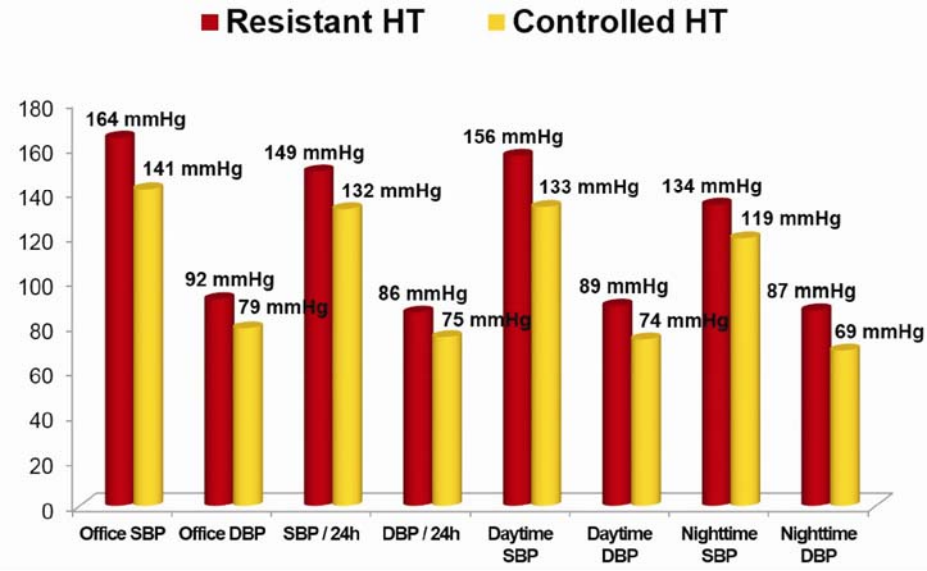

Figure 4. Office blood pressure values and ABPM data in resistant and controlled hypertension.

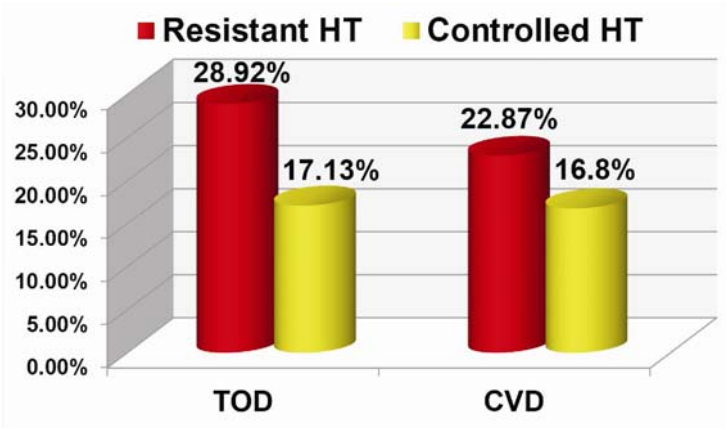

Figure 5. TOD and CVD in patients with resistant and controlled HT.

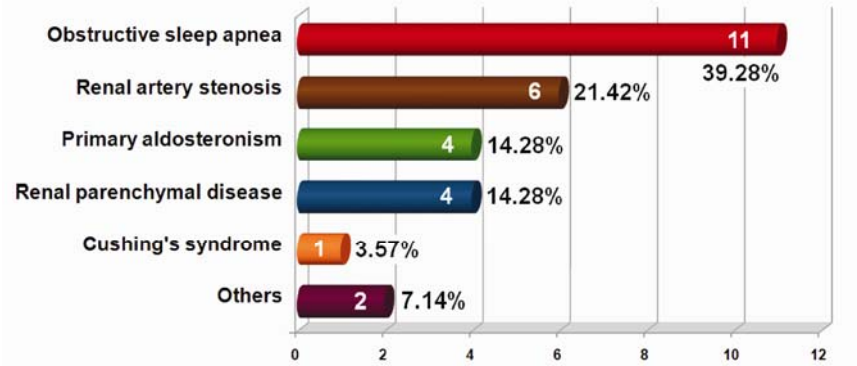

Figure 6. Etiology of secondary hypertension.

The antihypertensive treatment was administrated in 70% of patients in the morning. The analysis of antihypertensive drug classes showed differences between patients with resistant hypertension and controlled hypertension. True resistant hypertension patients, versus controlled hypertension, received more often renin-angiotensin system blockers (79.6% *versus* 67.5%), calcium channel blockers (54.6% *versus* 28%), diuretics 100% *versus* 39%, and other classes (47.5% versus 5.3%), but less β-blockers, $p<0.001$ for all comparisons (Figure 7).

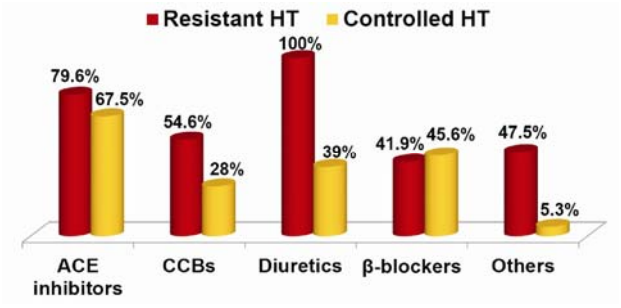

Figure 7. Antihypertension therapy in resistant and controlled hypertension.

Discussions

Studies have demonstrated that resistant hypertension is an increasingly common problem in hypertension and may affect as many as 15–20% of the hypertensive population [3]. The prevalence depends on the definition used for resistant hypertension, characteristics of the study population and methodology of study and is between 5% (trials in primary care) to 20-30% in hypertension and nephrology clinics [4–6]. In our study, of a selected study population (appreciated initially as adherent to treatment by their family doctors), based on office blood pressure measurements, the prevalence of resistant hypertension was 14.84%. After exclusion of the "white-coat effect" by AMBP, prevalence was 9.37% and after excluding pseudo-resistant and secondary hypertension, true resistant hypertension was present in only 7.17%. It is crucial to exclude pseudo-resistance resulting from failure of the patient to adhere to treatment regimens and by the concomitant use of drugs that may interfere with the prescribed antihypertensive agents [6].

In Romania, the SEPHAR II trial, based only on OBP, confirmed that 27.68% of the treated patients performed the criteria of resistant hypertension. Pseudo-resistant hypertension and the "white-coat effect" were not excluded, so that the real prevalence of true resistant hypertension is appreciated as being smaller [7, 8]. From the data of the Spanish Society of Hypertension on 68045 patients which performed ABPM, prevalence of resistant hypertension was 12.2% [9]. Studies have demonstrated that the prevalence of resistant hypertension is growing, concomitant with the higher prevalence of obesity, diabetes, sleep apnea and aging of the population.

Pseudo-resistant hypertension had in our study a prevalence of 17.08%. The causes of pseudo-resistant hypertension are presented in Figure 8.

Poor adherence to treatment had the following causes: secondary effects of the drugs, a great number of tablets administrated daily, high costs of the medication, lack of education of the patient concerning the disease and an inappropriate relation with the doctor and nurse [10, 11]. Non-adherence had in our study an incidence, of 17 %, as we evaluated it only by discussions with the patients and their families and not by titration of drugs concentrations. Studies have demonstrated that adherence can be improved by selecting well tolerated medications with once a day administration, by a better communication with the patient and medical education [6, 12]. The RESIST-POL Study demonstrated a low adherence to treatment by drug titration, based on the fact that only 13.9% of the patients had drugs concentrations over the limit of quantification, 86.1% presented at least one drug under this limit and 13.9% had no detectable drug in the blood [13]. To determine the prevalence of true resistant hypertension, titration of the drug concentrations is needed in future studies.

The factors implicated in resistant hypertension are important to be detected, as they can be removed [1, 10, 14]. Obesity produces resistant hypertension by associating excessive sodium retention, sympathetic stimulation, activation of the renin-angiotensin system, resistance to insulin and sleep apnoea. Many studies have shown that till 40% of patients with resistant hypertension are obese and that weight loss will reduce moderately hypertension [15]. High alcohol consumption is associated with increased blood pressure, stroke risk and a worse outcome. Stopping excessive alcohol consumption can lower mean SBP with 7.2 mmHg and mean DBP with 6.6 mmHg [1,10].

Excessive salt intake (more than 6 g/day) is known as favouring resistant hypertension. The majority of patients with resistant hypertension consume much salt, often over 10 g/day. This effect is greater in individuals sensible to salt, especially elderly, with obesity and kidney disease. Besides increasing blood pressure, salt lowers the antihypertensive effect of the drugs. By measurement of 24 hours urinary sodium, patients with a high sodium intake can be detected, as their urinary sodium excretion exceeds 100 mmol /24h [2, 5].

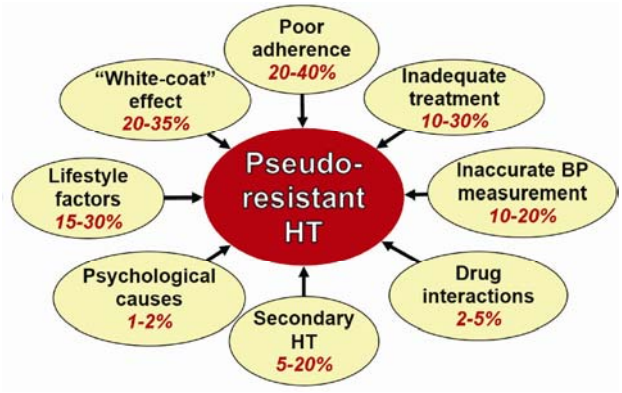

Figure 8. Causes of pseudo-resistant hypertension.

A small number of patients (2%) take drugs that can increase blood pressure as non-steroidal anti-inflammatory agents, aspirin, oral contraceptives, amphetamines, gluco- and mineralocorticoids, nasal drops, liquorice, etc. The effects of these drugs can differ from one patient to the other, in some being smaller, in others more important. Usual non-steroidal anti-

inflammatory agents increase blood pressure with a mean of 5 mmHg and lower the effect of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, but not that of calcium channel blockers. Non-steroidal anti-inflammatory drugs inhibit the renal production of E2 and E12 prostaglandins, therefore the patients with diabetes and renal diseases are at high risk [5, 16].

Volume overload that contributes to resistant hypertension can be secondary to the reduction of the renal filtration rate, inadequate diuretic therapy or secondary to a vasodilator therapy [2, 17].

The correct diagnosis of resistant hypertension imposes the exclusion of secondary hypertension. The incidence of secondary hypertension was in our study 6.37%, as we included from the beginning patients appreciated as having essential hypertension. The prevalence of secondary hypertension is higher in specialized centres, up to 10–20% [12, 18]. From 4000 patients with resistant hypertension, evaluated over a period of 18 years in a hypertension clinic, 10% of all and 17% of those over 60 years had secondary hypertension [14]. Studies have shown a frequent association between primary hyperaldosteronism, obesity and sleep apnea [11].

In our experience, the control of hypertension was underestimated in one third of patients, who had high OBP due to a "white-coat effect". The family practitioner must be aware of this possibility and evaluate these patients with ABPM.

Resistant hypertension identifies a subgroup of patients with high risk of subsequently cardiovascular events as myocardial infarction, stroke, heart failure, chronic kidney disease and a higher mortality risk. These complications reinforce the diagnosis of resistant hypertension and influence the treatment. Many trials showed that the cardiovascular risk is 2–4 times higher in resistant hypertension, which develops 50% more cardiovascular events in a follow up period of 3.8 years, compared to controlled hypertension [1, 12, 19].

Therapy recommendations in resistant hypertension include drug combinations with different mechanisms of action, administrated in optimal doses [1, 2, 18]. A volume overload can be reduced by dual diuretic therapy (thiazide and aldosterone receptor antagonist). The reduction of vascular resistance can be obtained by blocking the renin-angiotensin system, relaxation of blood vessel walls by calcium channel blockers, α blockers and direct vasodilators. Using adequate interventions in a short period of time a good control of blood pressure can be obtained in 50% of patients with resistant hypertension [18].

If blood pressure values are over the guidelines targets after 3–6 months of therapy, patients must be directed to specialists for a more complex evaluation and therapy. Catheter-based renal denervation is recommended only in cases of resistant hypertension with SBP over 160 mmHg and DBP over 100 mmHg. The evaluation of efficacy of the renal denervation, compared with medical treatment, needs further studies [1,18].

The data observed in our study are not representative for the whole hypertensive population of Romania, as they reflect especially experience in primary care settings.

Conclusions

After this study, resistant hypertension is better known and managed by our family doctors. The prevalence of true resistant hypertension was 7.17%. Before confirming true resistant hypertension, we must exclude a "white-coat effect", pseudo-resistance or secondary hypertension. True resistant hypertension was associated with higher BP values, older age of the patients, a longer duration of hypertension, obesity, diabetes, metabolic syndrome, multiple risk factors, target organ damage and cardiovascular diseases. Patients with resistant hypertension must be intense treated, combating the pathologic mechanisms implicated. Considering the unfavourable prognosis of resistant hypertension, the increased effort of the general physicians for improving this condition is fully justified.

Conflict of interest

The authors disclose no conflict of interest.

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