

# Profile of patients with resistant hypertension

## Profil chorych z nadciśnieniem tętniczym opornym

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### Abstract

**Introduction.** Resistant hypertension (RHT) is recognized when the blood pressure (BP) is equal to or greater than 140/90 mmHg, despite changes in lifestyle and using at least 3 antihypertensive drugs, including diuretics at optimal doses. Often, patients limit the proper control of BP by voluntary reduction and discontinuation of less tolerated drugs, failure to follow healthy lifestyle rules, and taking medications that increase BP. The reason for the lack of effects in treatment of hypertension (HT) is also unrecognized secondary HT.

The aim of the study is to evaluate the occurrence of pseudo-RHT in patients with primary RHT diagnosis.

**Material and methods.** The study was conducted in 2012–14 among patients hospitalized in the Department of Cardiology of The Pope John Paul II Province Hospital in Zamość. 99 patients diagnosed with RHT were examined, (59 men) at age 54.5–67.0 on average 60.0 ± 9.8 years. Statistical analysis was performed based on Statistica; Chi2 and U-Mann-Whitney tests were used.

**Results.** The final group consisted of 93 people (55 men). In the course of hospitalization, studies were conducted for secondary causes of HT. Efficacy of treatment was evaluated, education on healthy lifestyle was conducted and in some cases pharmacotherapy was modified. As a result of the diagnostic procedure and increased control of applied therapy, 30 patients with true RHT and 63 patients with pseudo-RHT were identified from a group of 93 patients with initial RHT. Patients with true RHT (16 men) were proposed renal artery denervation.

**Conclusions.** A large group of patients with diagnosed RHT are patients with pseudo-RHT. The common cause of RHT is the presence of an undetected secondary HT.

**Key words:** true resistant hypertension, pseudo-resistant hypertension

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### Streszczenie

**Wstęp.** Nadciśnienie tętnicze odporne (RHT, *resistant hypertension*) rozpoznaje się, gdy ciśnienie krwi (BP, *blood pressure*) jest większe lub równe 140/90 mmHg, mimo zmiany stylu życia i stosowania co najmniej 3 leków przeciwnadciśnieniowych, w tym diuretyków, w optymalnych dawkach. Często pacjenci utrudniają osiągnięcie prawidłowej kontroli BP przez samowolne zmniejszanie dawki lub odstawianie gorzej tolerowanych leków, nieprzestrzeganie zaleceń dotyczących zdrowego stylu życia lub przyjmowanie leków zwiększających BP. Przyczyną nieskuteczności leczenia nadciśnienia tętniczego (HT, *hypertension*) może być również nierozpoznane wtórne HT.

Badanie przeprowadzono w celu oceny częstości występowania rzekomoopornego nadciśnienia tętniczego u chorych z pierwotnym rozpoznaniem RHT.

**Materiały i metody.** Badanie przeprowadzono w latach 2012–2014 wśród chorych hospitalizowanych na Oddziale Kardiologii Szpitala Wojewódzkiego im. Jana Pawła II w Zamościu. Zbadano 99 chorych (59 mężczyzn) z rozpoznaniem RHT w wieku 54,5–67,0 lat (średnia wieku 60,0 ± 9,8 r.).

Analizy statystyczne przeprowadzono, korzystając z oprogramowania Statistica; wykonano test Chi<sup>2</sup> i test U Manna-Whitneya.

**Wyniki.** Ostatecznie badana grupa składała się z 93 chorych (55 mężczyzn). W trakcie hospitalizacji u chorych wykonano badania pod kątem przyczyn wtórnego HT. Oceniono skuteczność leczenia, przeprowadzono edukację

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chorych odnośnie do zdrowego stylu życia, a w niektórych przypadkach zmodyfikowano leczenie farmakologiczne. Po przeprowadzeniu badań diagnostycznych oraz zweryfikowaniu stosowanego leczenia w grupie 93 chorych z pierwotnym rozpoznaniem RHT zidentyfikowano 30 chorych z rzeczywistym RHT i 63 chorych z rzekomoopornym HT. Chorym z rzeczywistym RHT (16 mężczyzn) zaproponowano denerwację tętnic nerkowych.

**Wnioski.** Dużą grupę chorych z rozpoznaniem RHT stanowią pacjenci z rzekomoopornym HT. Częstą przyczyną RHT jest obecność niewykrytego wtórnego HT.

**Słowa kluczowe:** rzeczywiste nadciśnienie tętnicze oporne, rzekomooporne nadciśnienie tętnicze

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## Introduction

Resistant hypertension (RHT) is recognized when the blood pressure (BP) is equal to or greater than 140/90 mmHg, despite lifestyle modifications and the use of at least 3 antihypertensive drugs, including diuretics at optimal doses [1]. It is estimated that the problem of resistance affects 10–13% of the HT population. It is particularly important because of the much higher cardiovascular risk in this group of patients [2]. The reasons for lack of response to antihypertensive treatment may vary. In some patients it is not possible to determine the reasons for the resistance based on the available diagnostic methods, while in the remaining cases the RHT is diagnosed despite a detectable cause [3]. A common reason is the use of an inadequate treatment regimen resulting from too low doses of medication and lack of diuretics in combination therapy. Patients limit the proper control of BP by voluntary reduction and discontinuation of less tolerated drugs. Neglecting the principles of healthy lifestyle such as weight reduction, sodium and alcohol intake and insufficient physical activity also play an important role. It is worth noting that taking certain medications (glucocorticosteroids, non-steroidal anti-inflammatory drugs, contraceptives) may cause an increase in BP [4]. Ineffective HT treatment is also caused by unrecognised secondary HT in renal disease, renal artery stenosis, endocrine diseases, organic cardiovascular disease, obstructive sleep apnea, and others [5].

Very often the high BP values are caused by over-stress during medical examinations, with normal BP values measured at home. This is the so-called “white coat” hypertension and it is referred to as pseudo-RHT.

It is important to be aware of the possible causes of ineffectiveness of HT treatment. The aim of this study is to evaluate the occurrence of pseudo-RHT in patients with primary RHT diagnosis.

## Materials and methods

The study was conducted in 2012–14 among patients hospitalized in the Department of Cardiology of The Pope John Paul II Province Hospital in Zamość. The study group initially consisted of 99 patients (59 men) aged 54.5–67.0 on average  $60.0 \pm 9.8$  years. All patients were referred from specialized cardiac or medical clinics with RHT diagnosis. The purpose of hospitalization was to carry out extended diagnostic tests for secondary HT, drug intake and qualification for possible renal artery irregularity following RHT confirmation. During hospitalization, patients had basic laboratory tests such as complete blood count, electrolyte levels, renal indexes, urinalysis, fasting glucose levels. In addition, the thyroid hormone level, the daily cortisol profile, 24-hour urinary metanephrine, the aldosterone-renin index were determined. Basic imaging tests were performed such as abdominal ultrasound, renal artery flow using Doppler method and, in some cases, abdominal CT scan.

The incidence of true and pseudo-RHT in the group primarily diagnosed with RHT was analyzed. Patients with true RHT were qualified for renal artery denervation. Statistical analysis was performed based on Statistica; Chi<sup>2</sup> and U-Mann-Whitney tests were used.

## Results

The study group finally consisted of 93 people (55 men), because 6 patients (6.1% of the respondents) did not report to the hospital within the agreed time without giving a reason. The course of qualification of patients with initial RHT diagnosis for renal artery denervation is presented in Table I.

At the interview stage, it was determined that 8 patients (i.e. 8.6% hospitalized) did not receive regular antihypertensive medication or only took some of the prescribed medications. Two of the others

**Table I.** Qualification of patients with primary diagnosis of RHT for renal arterial denervation

Stage	Number of patients (n)	Reason for disqualification	Disqualified n, (%)*, (%)**	Other n, (%)***
1	99	They did not present for the initial test	6 (6.1)	93 (93.9)
2	93	Irregular outpatient treatment	8 (8.6), (8.6)	85 (85.8)
3	85	Previously recognized secondary HT	2 (2.3), (2.2)	83 (83.8)
4	83	No technical feasibility of the procedure	5 (6.0), (5.4)	78 (78.8)
5	78	Secondary HT diagnosed during hospitalization	24 (30.8), (25.8)	54 (54.5)
6	54	Positive BP control in ambulatory settings	24 (44.4), (25.8)	30 (30.3)
7	30	No consent to surgery	15 (50.0), (16.1)	15 (15.1)****

\*percentage of the number of patients at the previous stage

\*\*percentage of the number of hospitalized patients

\*\*\*number of patients in the subsequent stages of the qualification and percentage of the patients reported

\*\*\*\*number and percentage of patients who underwent the procedure

**Table II.** General characteristics of hospitalized patients with suspected RHT. Sociodemographic and disease data

Sociodemographic data	Total n = 93 (100,0%)	Patients with true RHT n = 30 (32.3%)	Patients with pseudo-RHT n = 63 (67.7%)	p*
Male gender	55 (59.1)	16 (53.3)	39 (61.9)	0.4318
Age (years)	60.1 (± 10.0)	58.8 (7.1)	60.7 (11.2)	0.1535
Place of residence — city	51 (54.8)	17 (56.7)	34 (54.0)	0.8069
Duration of HT (years)	11.9 (± 6.0)	12.0 (± 5.5)	11.8 (± 6.3)	0.9570
Number of antihypertensive drugs	4.6 (± 0.9)	5.1 (± 0.8)	4.4 (± 0.9)	0.0012
BMI [kg/m <sup>2</sup> ]	31.4 (± 4.6)	32,6 (± 4,6)	30.8 (± 4.6)	0.0453
Diabetes	32 (34.4)	11 (36,7)	21 (33.3)	0.7518
Past stroke	13 (44.0)	5 (16,7)	8 (12.7)	0.6059
Coronary disease	22 (23.7)	7 (23,3)	15 (23.8)	0.9597

Data is presented as n-number of patients (percentage) or mean value (± SD)

\*p for the Chi<sup>2</sup> test or the Mann-Whitney U test

reported had previously identified secondary HT (renal artery stenosis and polycystic kidney disease).

In the course of hospitalization, studies were conducted for secondary causes of HT, efficacy of treatment was assessed, education on healthy lifestyle was conducted and in some cases pharmacotherapy was modified. After receiving the results, 24 patients (25.8% hospitalized) with suspected secondary HT due to reasons such as renal artery stenosis (n = 11), primary hyperaldosteronism (n = 7), pheochromocytoma (n = 2), hypercortisolemia (n = 2), hyperthyroidism (n = 1) and hyperparathyroidism (n = 1) were recognised. Some of these patients required further diagnostics and specialized treatment. After about a month of hospitalization, patients had a Cardiology Clinic visit combined with Ambulatory Blood Pressure Monitoring (ABPM). During this visit, another 24 patients (25.8% hospitalized) showed satisfactory BP control confirmed by ABPM.

The reason for acquiring the target BP values could have been a lifestyle change, a previous modification of the treatment, and/or a regular intake of prescribed medications. From the group of 93 patients with initial RHT a total of 30 patients (32.3%) with true RHT and a group of 63 (67.5%) with pseudo-RHT were identified as a result of a diagnostic procedure and an increase in the control of applied therapy. Patients with true RHT (16 males) were proposed for renal artery denervation; half of the respondents agreed.

Sociodemographic data and morbidity in patients with true and pseudo-RHT are presented in Table II. The groups did not differ in terms of gender, age, place of residence, duration of HT and incidence of diabetes, stroke and coronary heart disease. Patients with true RHT took more medications (5.1 vs. 4.4; p = 0.0012). Statistically significant higher body mass index (BMI) occurred in patients in this group (32.6

**Table III.** General characteristics of hospitalized patients with suspected RHT. Laboratory tests

Laboratory tests	Total n = 93 (100,0%)	Patients with true RHT n = 30 (32.3%)	Patients with pseudo-RHT n = 63 (67.7%)	P*
Hgb [g/dL]	13.8 (± 1.4)	13.9 (± 1.3)	13.7 (± 1.4)	0.6247
RBC [mln/uL]	4.6 (± 0.5)	4.6 (± 0.5)	4.5 (± 0.5)	0.4301
WBC [K/uL]	7.4 (± 1.9)	7.6 (± 1.8)	7.3 (± 1.9)	0.2927
PLT [K/uL]	204.7 (± 47.8)	198.5 (± 38.3)	207.7 (± 51.7)	0.6721
CREAT [mg/dL]	1.0 (± 0.3)	1.0 (± 0.3)	1.0 (± 0.3)	0.2349
K+ [mmol/L]	4.2 (± 0.5)	4.3 (± 0.4)	4.2 (± 0.5)	0.4619
NA+ [mmol/L]	140.4 (± 2.5)	139.7 (± 2.8)	140.8 (± 2.3)	0.0637
Uric acid [mg/dL]	6.1 (± 1.4)	6.0 (± 1.6)	6.2 (± 1.3)	0.6631
Urea [mg/dL]	42.0 (± 12.7)	37.7 (± 11.1)	44.0 (± 13.0)	0.0235
Proteinuria (+)	14 (15.1)	7 (23.3)	7 (11.1)	0.1234

Data is presented as n-number of patients (percentage) or mean value (± SD)  
\*p for the Chi<sup>2</sup> test or the Mann-Whitney U test

vs. 30.8;  $p = 0.0453$ ). The results of laboratory tests are presented in Table III. There was a statistically significant lower level of urea in patients with true RHT and a statistically significant low sodium level in this group.

## Discussion

The causes of resistance to HT treatment are very different. Attention should be paid to the diagnostic insight as up to 24 cases (25.8% of patients) in our study were diagnosed with secondary HT. The most common cause was renal artery stenosis in 11.8% of patients and another was primary hyperaldosteronism in 7.5% of patients. The results obtained are consistent with literature data, where renal artery stenosis is also listed as one of the major causes of secondary HT, amongst renal parenchymal disease and primary hyperaldosteronism [6]. It is noted that the proportion of secondary HT was more frequent in the study group compared to earlier publications, where 5% of the subjects had secondary HT in the RHT group [7]. This difference is due to the limited possibility of conducting diagnostic tests in ambulatory conditions in patients with previous diagnosis of secondary HT, hence the diagnosis was established only during hospitalization.

The key role in treatment of HT is the compliance of the patient with the doctor's instructions and adherence to their medical advice. It has been recognized since 2003 in the World Health Report as an important factor responsible for the outcome of HT treatment and includes patient's compliance with recommendations about lifestyle and regular

medication intake. Another issue is the improper treatment that results from a physician's attitude and failure to achieve therapeutic goals due to the lack of dose modifications and not adjusting the amount of medications. This is the so-called therapeutic inertia. Its causes should be sought in the lack of knowledge of target BP values, in the fear of too low BP values and the belief that the patient will not accept more medication [8, 9].

Our research shows that the common cause of the lack of proper BP control is the non-compliance with the recommended regimen. At the time of admission to the hospital, it was found that 8 patients (8.6%) did not take the recommended medicines. Another 24 patients (25.8%) after hospital stay and slight modification of treatment received a normal BP during a follow-up visit and in ABPM measurements. In the study cited, 58% of patients used an inadequate treatment regimen with too low doses of diuretics and 16% of patients did not comply with the medical advice [7].

In our analysis, true RHT was present in 30% of patients with primary RHT diagnosis. Amongst this group, patients were found to have significantly higher body mass and BMI which demonstrates their negligence towards lifestyle modifications, including weight reduction. Patients with RHT received significantly greater antihypertensive drugs dose; yet, they failed to maintain proper BP control.

In evaluating patients with RHT in many previous studies, it appeared that important predictors of BP control failure were age greater than 75 years, left ventricular hypertrophy and obesity with a BMI above 30 kg/m<sup>2</sup> [10]. Patients with RHT were characterized by a higher incidence of organ damage [11].

In our study group of patients with RHT, proteinuria also appeared more frequently as an indication of renal failure. There was no increased incidence of diabetes in patients. Also, RHT occurrence was not found to be more common in the elderly.

The study showed that we often encounter pseudo-HT resistance. Employing appropriate treatment regimens with proper antihypertensive doses and patient adherence to treatment recommendations and lifestyle modifications significantly reduce the number of RHT patients. It is necessary to pay close attention to the cooperation between the doctor, the district nurse and the patient in order to achieve better HT treatment results. Another important problem is still a large number of unrecognized secondary HT forms that can be effectively treated.

### Conclusions

1. A relatively large group of patients with recognized RHT does not meet the diagnostic criteria and these are patients with pseudo-RHT.
2. The common cause of RHT is the presence of an undetected secondary HT, diagnostic caution in treating patients with RHT should be maintained.

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