ISSN 1607-419X
ISSN 2411-8524 (Online)
УДК 616.12-008.331.1-07

Definition and diagnosis of resistant hypertension: search for a joint decision

Yu. I. Grinshtein, V. V. Shabalin

Krasnoyarsk State Medical University named after Professor V. F. Voyno-Yasenetsky, Krasnoyarsk, Russia

Corresponding author:
Yurii I. Grinshtein,
MD, PhD, Professor, Krasnoyarsk State Medical University named after Professor V.F. Voyno-Yasenetsky, 1 Partisan Zheleznyak street, Krasnoyarsk, 660022 Russia.
E-mail: grinstein.yi@mail.ru

Received 28 May 2014;
accepted 30 August 2014.

Abstract

Resistant hypertension is defined as uncontrolled blood pressure on optimal doses of three antihypertensive agents, including a diuretic. According to the data from different studies, its prevalence achieves 10–15%. The up-to-date approaches to classification, diagnostic algorithms are discussed; the reasons of resistant hypertension are reviewed. Special attention is paid to the opportunities of ambulatory blood pressure monitoring in distinguishing particular forms of resistant hypertension and pseudoresistant hypertension; a specific diagnostic algorithm is presented.

Key words: arterial hypertension, resistant hypertension, pseudoresistant hypertension, ambulatory blood pressure monitoring

For citation: Grinstein YuI, Shabalin VV. Definition and diagnosis of resistant hypertension: searching for joint decision. Arterial'naya Gipertenziya = Arterial Hypertension. 2014;20(6):546–552.

Определение и диагностика резистентной гипертензии: в поиске согласованных решений

Ю. И. Гринштейн, В. В. Шабалин

Государственное бюджетное образовательное учреждение высшего профессионального образования «Красноярский государственный медицинский университет имени профессора В. Ф. Войно-Ясенецкого» Министерства здравоохранения Российской Федерации, Красноярск, Россия

Контактная информация:
Гринштейн Юрий Исаевич,
ГБОУ ВПО «Красноярский государственный медицинский университет имени профессора В.Ф. Войно-Ясенецкого» Минздрава России, ул. Партизана Железняка, д. 1, Красноярск, Россия, 660022.
E-mail: grinstein.yi@mail.ru

Статья поступила в редакцию 28.05.14 и принята к печати 30.08.14.

Резюме

Резистентная гипертензия, распространенность которой достигает 10–15% по различным данным, представляет собой артериальную гипертензию, не контролируемую на фоне приема комбинации оптимальных доз трех антигипертензивных препаратов, одним из которых является диуретик. В обзорной статье обсуждаются современные подходы к классификации резистентной гипертензии, алгоритма диагностики, дифференциальной диагностике, а также возможные причины недостижения целевого уровня артериального давления и пути преодоления резистентности к терапии. Особое внимание уделяется возможностям суточного мониторирования артериального давления в выделении специфических форм резистентной гипертензии и псевдорезистентности, определении истинной резистентной артериальной гипертензии и приводится алгоритм диагностики.

Ключевые слова: артериальная гипертензия, резистентная гипертензия, псевдорезистентная гипертензия, суточное мониторирование артериального давления

Для цитирования: Гринштейн Ю.И., Шабалин В.В. Определение и диагностика резистентной гипертонии: в поисках согласованных решений. Артериальная гипертензия. 2014;20(6):546–552.

Introduction

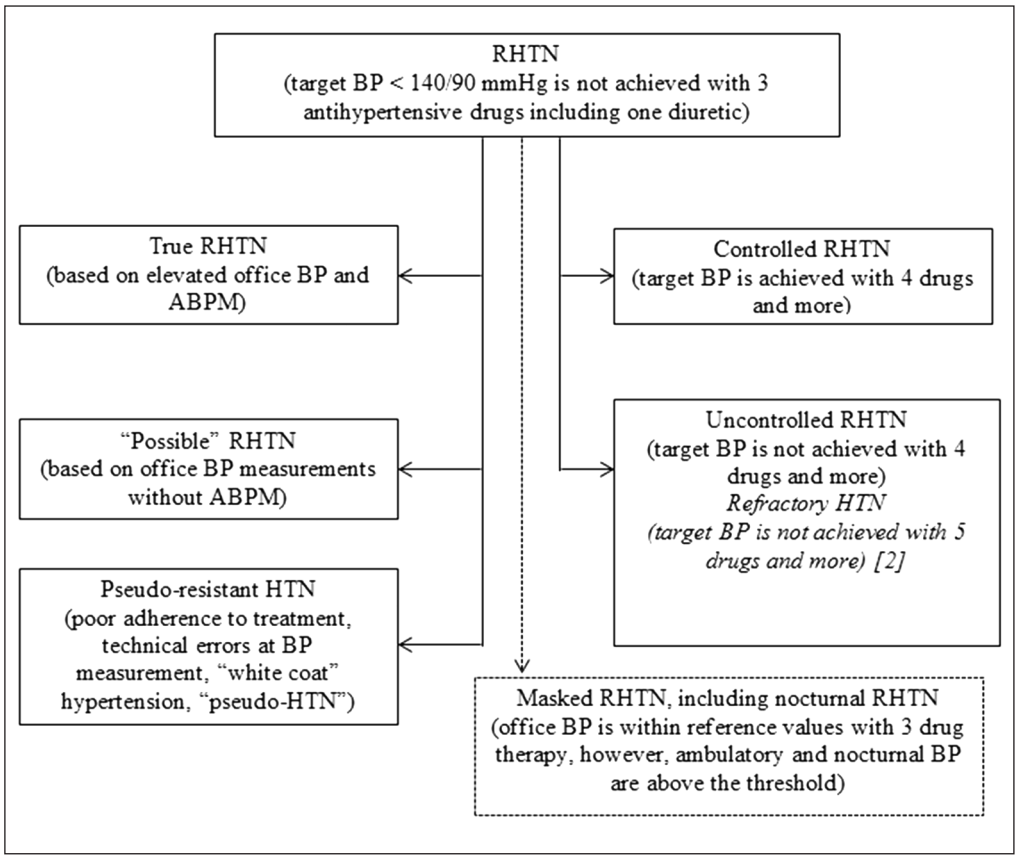
Systemic hypertension (HTN) is a serious medical and social problem of modern cardiology. Elevated blood pressure (BP) is an independent risk factor for cardiovascular diseases — coronary heart disease, myocardial infarction, congestive heart failure, stroke, and adverse outcomes. Resistant hypertension (RHTN) contributes to the development of adverse cardiovascular events. According to the conventional definition, hypertension is considered resistant to treatment if the target BP level is not achieved, despite the assignment of at least three drugs in optimal doses, including a diuretic, and lifestyle modification. If BP is controlled by four drugs or more, hypertension is called "controlled HTN" [1]. Thus, RHTN can be controlled if more medications are prescribed. Otherwise, resistant uncontrolled hypertension should be diagnosed. Later, the term "refractory hypertension" was proposed, and in March 2014 based on the results of a large-scale epidemiological study, a stricter definition of refractory hypertension was suggested, as following: BP > 140/90 mmHg, despite the use of more than 5 antihypertensives of different classes

(there were 78, or 0.5 %, patients out of 14809 that composed 3.6 % of all patients with RHTN, and 41.7 % of those treated with > 5 medications) [2]. Based on an analysis of > 600 000 hypertensives, the prevalence of RH was estimated as 14.8 % among treated patients and 12.5 % of all enrolled hypertensive patients [3]. However, available evidence of a higher predictive value of 24-hour monitoring of blood pressure (ABPM) compared to office BP led to the introduction of the term "true RHTN". It means a failure to reach target BP level based on the office measurements, 24-hour ambulatory BP measurements considering confirmed good adherence to the therapy. In contrast to the "true RHTN", the term "apparent RHTN" was suggested for the studies that did not imply 24-hour BP monitoring to exclude pseudo-resistant HTN [3]. Classification of different forms of RHTN is shown on Figure 1.

Based on the data from smaller studies, Judd E. and co-authors (2014) estimated true prevalence of RHTN equal to 10.1 % of treated patients and 7.9 % of all patients with hypertension (these correspond to about one half of the indicators based on office BP measurements alone) [3]. RHTN was more frequent in older age, males, patients with type 2 diabetes mellitus, obesity, chronic kidney disease [4, 5]. Patients with RHTN were shown to have 2-fold higher mortality, myocardial infarction, congestive heart failure, stroke, and renal disease, compared to patients with controlled BP [6]. A significantly higher frequency of subclinical organ damage, including left ventricular hypertrophy, increased carotid artery wall thickness, microalbuminuria, is an expected finding in RTN (as compared to non-resistant HTN) [7].

Pseudo-resistant hypertension can mask as RHTN. Its main reasons include technical errors in BP measurement (including small size of the cuff), poor adherence to the therapy, "white coat" HTN [8], and "pseudo-hypertension" caused by atherosclerosis and hypertrophy of arterial media, which mainly develops in elderly patients. In this case, an excessive effort is required to compress the brachial cuff at BP measurement that leads to an overestimation of the true BP level (intra-arterial

Figure 1. Types of resistant hypertension



Note: RHTN — resistant hypertension; HTN — hypertension; BP — blood pressure; ABPM — ambulatory blood pressure monitoring.

BP measurement is the most precise method in these cases). According to Kleman M. et al. (2013), "pseudo-hypertension" may account for about 7% of patients with RHTN [9].

In general, the number of patients with pseudo-resistant hypertension may reach 37–39% of all patients with RHTN [8, 10]. It is not surprising that patients with true RHTN have higher cardiovascular risk and more severe organ damage compared to the pseudo-resistant individuals [8, 10].

The widespread use of ABPM and home BP self-monitoring has allowed to define so-called masked hypertension characterized by normal office BP and elevated HTN according to ABPM, including nocturnal values. In our opinion, masked hypertension uncontrolled by three-drug combination therapy should be also considered as a resistant type (Figure 1 shows it in a dotted line, because officially it is not yet recognized as resistant HTN). According to the recent (2013) International ABPM recommendations, treated HTN characterized by normal office BP and high ambulatory BP should be designated as "masked uncontrolled HTN" [11–13]. Based on the largest Spanish Registry (62 788 patients with HTN), masked HTN may account for 31.1% of patients receiving antihypertensive therapy who have target office BP, but elevated ABPM values [14]. According to the same Registry, the prevalence of masked hypertension was mostly due to the inadequate nocturnal BP reduction (the prevalence of "isolated nocturnal hypertension" was almost twice higher than the one of "isolated daytime hypertension", 24.3 vs. 12.9%). Considering that masked hypertension is frequently unrecognized (long-term prognosis in these patients is comparable to the outcomes in patients with elevated office BP), the recommendations ESH/ESC 2013 on the management HTN emphasized the need for ABPM in all patients with high normal office BP, normal office BP and asymptomatic end-organ damage, as well as in high risk individuals [15].

Today the prevalence of masked RHTN is underestimated. In a population Japanese study J-HOME Okawa T. et al (2006) found "isolated home resistant HTN" in 23.5% (office BP <140/90 mm Hg, home BP > 135/85 mm Hg, which corresponds to the term "masked RHTN") based on the office and home BP measurements in 528 patients with RHTN. Controlled hypertension was found in 17.8%, "isolated office RHTN" — in 16.1%, and "sustained RHTN" — in 42.6% [16].

To our knowledge, Muxfeldt E. S. and Salles G. F. were the first to use the term "masked RHTN" [17]. The authors identified 473 patients with RHTN based on office BP measurements, and then divided them into 4 groups according to ABPM and office BP: 1) fully controlled RHTN (office BP < 140/90 mm Hg, daytime BP < 135/85 mm Hg, nighttime BP < 120/70 mm Hg); 2) masked RHTN (office BP < 140/90 mm Hg, daytime BP > 135/85 mm Hg, and/or nighttime BP > 120/70 mm Hg); 3) RHTN with the phenomenon of "white coat HTN" (office BP > 140/90 mm Hg, daytime BP < 135/85 mm Hg, nighttime BP < 120/70 mm Hg); 4) true, uncontrolled RHTN (both office BP and ABPM levels are above the threshold). According to the 5-year follow-up, a group of masked RHTN consisted of 36 people (7.6% of total number of patients with RHTN), that is 38% of the patients with achieved target office BP < 140/90 mm Hg.

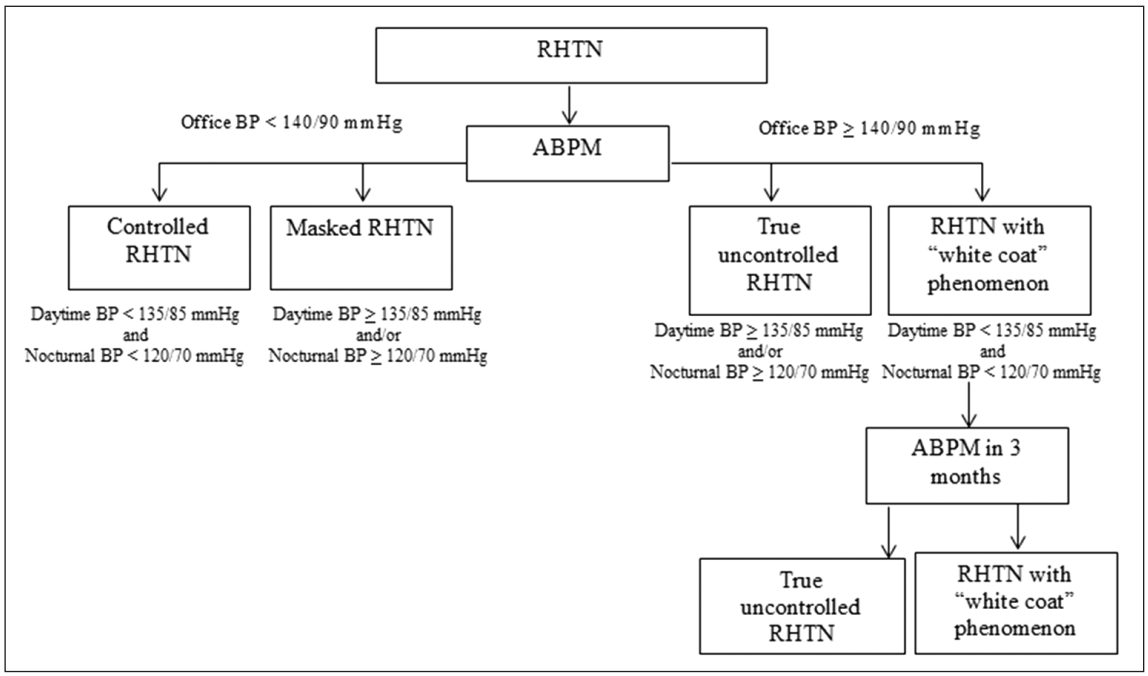
Taking into account that isolated nocturnal HTN is highly prevalent (approximately 7% of all hypertensive patients), and nocturnal BP have higher prognostic value compared to daytime BP [11], home self-monitoring BP is evidently unable to complete to replace ABPM. However, Chinese researchers Xu T. et al. (2013) attempted to compare BP values registered by ABPM and 6-times manual measurement BP at fixed times (22:00, 02:00, 6:00, 10:00, 14:00, 18:00) in 155 hypertensive in-patients. They did not find any statistical difference either in nocturnal BP, or in the rate of non-dipping profile [18]. However, we are convinced that the manual method of nocturnal BP measurements, due to its non-physiologic approach, cannot be considered an alternative.

Considering the high clinical value of ABPM in RHTN, Muxfeldt E. S. and Salles G. F. suggest the following algorithm for its use and data interpretation (cited with abridgements) (Fig. 2).

Causes of resistant hypertension

As mentioned above, the main causes of pseudo-resistant HTN include technical errors in the measurement of BP, poor adherence to treatment, "white coat" effect. After exclusion all these potential reasons, reversible causes of true RHTN

Figure 2. The interpretation of the data of ambulatory blood pressure monitoring in patients with resistant hypertension (cited according to Muxfeldt E.S. and Salles G.F., 2013)



Note: RHTN — resistant hypertension; BP — blood pressure; ABPM — ambulatory blood pressure monitoring.

should be found and eliminated, among them adverse lifestyle factors, some drugs and substances (the list is continuously updated, e. g. tyrosine kinase inhibitors [19], itraconazole [20]), and the screening for secondary HTN is also mandatory in patients with RHTN (Table).

Secondary HTN is known to be more frequent in individuals with RHTN compared to general hypertensive population, so just the presence of RHTN is an indication for screening. On the other hand, there is no consensus between experts whether primary or secondary HTN is predominant among patients with RHTN. Thus, according to the Russian study REGATTA-PRIMA, the rate of secondary HTN among patients with RHTN composed only 12 % [21]. At the same time, some foreign authors indicate predominantly secondary causes of RHTN. In our opinion, this divergence is due to an excessively broad interpretation of the concept of "secondary HTN", which includes, in addition to traditional forms (renal parenchymal HTN, renovascular, primary aldosteronism, etc.), those associated with obstructive sleep apnea (OSA), obesity, and metabolic syndrome (MS) [6]. In our opinion, primary HTN is more prevalent among patients with RHTN, however, common association with comorbidities aggravates its course and contributes to the development of drug-resistance. At the same time, novel understanding of the pathogenetic relation between OSA, obesity, MS, hyperaldosteronism, and resistant HTN demonstrates the importance of a detailed examination of patients with RHTN using techniques such as polysomnography, plasma aldosterone level assessment and, apparently, the ratio of plasma aldosterone/renin.

Based on polysomnography, OSA is detected in 70–90 % of patients with RHTN (in males), and the rate of moderate-to-severe cases achieve 50 % [6, 22]. OSA is associated with an increased sympathoadrenal activity, increased aldosterone excretion and endothelin-1. All these factors can to lead to an increase in BP. Aldosterone can exacerbate the degree of upper airway obstruction due to chronic parapharyngeal fluid retention [6].

In turn, visceral fat obesity, and MS also lead to an excessive aldosterone secretion. Thus, a common co-existence of OSA, obesity, MS, and hyperaldosteronism in patients with RHTN is not surprising, and overproduction of aldosterone is a link in their interaction [6].

Table

POSSIBLE CAUSES OF TRUE RESISTANT HYPERTENSION

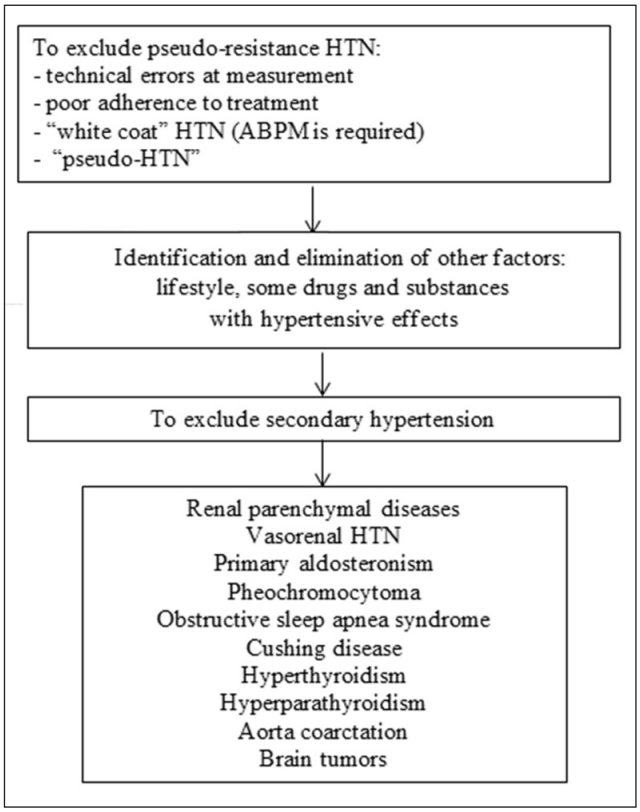
Lifestyle factors
Obesity Excessive salt intake alcohol abuse
Medications and other substances with potential hypertensive effect
Nonsteroidal anti-inflammatory drugs Sympathomimetics (ephedrine, decongestants) Stimulants (amphetamine, methamphetamine, modafinil) Oral contraceptives Glucocorticoids Cyclosporine Erythropoietin Licorice Coke Tyrosine kinase inhibitors [20], Itraconazole [21]
Secondary hypertension
Renal parenchymal disease Renovascular hypertension Primary hyperaldosteronism Pheochromocytoma Obstructive sleep apnea Cushing disease Hyperthyroidism Hyperparathyroidism Aorta coarctation Brain tumors

Recommended algorithm for true RHTN verification is summarized on Figure 3.

Conclusions

For the recent years there has been a significant expansion of our understanding of the prevalence, poor prognosis in RHTN, high rate of "pseudo-resistance", heterogeneity of the "true RHTN", and the difficulties of its identification by office or home BP measurements without ABPM. As ABPM became more available in routine clinical practice, classification of RHTN was updated. At the same time, the issues of RHTN diagnostics are still unsolved, and the search for concerted solutions is ongoing.

Figure 3. The algorithm of verification of resistant hypertension origin



Note: RHTN — resistant hypertension; HTN — hypertension; BP — blood pressure; ABPM — ambulatory blood pressure monitoring.

Conflict of interest
The authors declare no conflict of interest.

References

1. Calhoun DA, Jones D, Textor S et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117(25):510–26.

2. Calhoun DA, Booth JN, Oparil S et al. Refractory hypertension: determination of prevalence, risk factors, and comorbidities in a large, population-based cohort. Hypertension. 2014;63(3):451–8.

3. Judd E, Calhone DA. Apparent and true resistant hypertension: definition, prevalence and outcomes. J Hum Hypertens. 2014;28(8):463–8.

4. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. 2012;125(13):1635–42.

5. Sim JJ, Bhandari SK, Shi J, Liu IL, Calhoun DA, McGlynn EA et al. Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. Mayo Clin Proc. 2013;88 (10):1099–1107.

6. Dudenbostel T. Resistant hypertension — complex mix of secondary causes and comorbidities. J Hum Hypertens. 2014;28(1):1–2.

7. Muxfeldt ES, de Souza F, Margallo VS, Salles GF. Cardiovascular and renal complications in patients with resistant hypertension. Curr Hypertens Rep. 2014;16 (9):471.

8. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011;57(5):898–902.

9. Kleman M, Dhaniamraji S, Difillippo W. Prevalance and characteristics of pseudohypertension in patients with "resistant hypertension". J Am Soc Hypertens. 2013;7 (6):467–70.

10. Brambilla G, Bombelli M, Seravalle G, Cifkova R, Laurent S, Narkiewicz K et al. Prevalence and clinical characteristics of patients with true resistant hypertension in central and Eastern Europe: data from the BP-CARE study. J Hypertens. 2013;31(10):2018–24.

11. O'Brien E, Parati G, Stergiou G. Ambulatory blood pressure measurement: what is international consensus? Hypertension. 2013;62(6):988–94.

12. Crespo JJ, Fabbian F, Haus E, Manfedini R et al. 2013 ambulatory blood pressure monitoring recommendations for the diagnosis of adult hypertension, assessment of cardiovascular and other hypertension-associated risk, and attainment of therapeutic goals. Chronobiol Int. 2013;30 (3):355–410.

13. Hermida RC, Smolensky MH, Ayala DE et al. 2013 ambulatory blood pressure monitoring recommendations for the diagnosis of adult hypertension, assessment of cardiovascular and other hypertension-associated risk, and attainment of therapeutic goals. Chronobiol Int. 2013;30 (3):355–410.

14. Banegas JR, Ruilope LM, de la Sierra A, de la Cruz JJ, Gorostidi M, Segura J et al. High prevalence of masked uncontrolled hypertension in people with treated hypertension. Eur Heart J. 2014. doi: 10.1093/eurheartj/ehu016. [Electronic resource]. URL: http://eurheartj.oxfordjournals.org/content/early/2014/02/03/eurheartj.ehu016.abstract. Checked: 25.05.2014.

15. Mancia G, Fagard R, Narkiewicz K et al. 2013 practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2013;31 (10):1925–38.

16. Okawa T, Obara T, Ohkubo T et al. Characteristics of resistant hypertension determined by self-measured blood pressure at home and office blood pressure measurements: the J-HOME study. J Hypertens. 2006;24(9):1737–43.

17. Muxfeldt ES, Salles GF. How to use ambulatory blood pressure monitoring in resistant hypertension. Hypertens Res. 2013;36(5):385–9.

18. Xu T, Zhang Y, Xuerui T. Estimate of nocturnal blood pressure and detection of non-dippers based on clinical or ambulatory monitoring in the inpatient setting. BMC Cardiovasc Disorders. 2013;13:37.

19. Weber F, Anlauf M. Treatment resistant hypertension — investiagation and conservative management. Dtsch Arztebl Int. 2014;111(25):425–31.

20. Denolle T, Azizi M, Massart C, Zennaro MC. Itraconazole: a new drug-related cause of hypertension. Ann Cardiol Angeiol. (Paris). 2014;63(3):213–5.

21. Chazova IE, Fomin VV, Razuvaeva MA. Resistant and uncontrolled arterial hypertension: a challenge of XXI century. RHarmateka. 2011;218(5):3–8. In Russian.

22. Muxfeldt ES, Margallo VS, Guimaraes GM. Prevalence and associated factors of obstructive sleep apnea in patients with resistant hypertension. Am J Hypertens. 2014;27(8):1069–78.