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Case report

RESISTANT HYPERTENSION WITH CORONARY ARTERY DISEASE

РЕЗИСТЕНТНА ХИПЕРТЕНЗИЈА СО КОРОНАРНА АРТЕРИСКА БОЛЕСТ

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Abstract

Resistant hypertension is encountered in around 30% of hypertension population and it requires at least four antihypertensive medications for treatment. It is associated with cardiovascular (CV) events. Resistant hypertension often occurs as a comorbidity with coronary artery disease, so quantification of total CV risk, which is best done with the SCORE system, is important for risk stratification of hypertensive patients in order to implement therapy to reduce the cardiovascular risk.
In this study, we report clinical findings of a 66-year-old woman presenting with resistant hypertension and coronary artery disease, her hospital treatment and recommendation for home treatment after being discharged from hospital. Further we discussed the recent guidelines diagnostic and treatment algorithms.
In conclusion, hypertension is the most common risk factor in patients with coronary vascular disease and its regulation, especially in the resistant form, is one of the most important factors for reducing the prevalence of coronary artery disease as well as the degree of major adverse cardiovascular events in patients with existing coronary artery disease.

Keywords: resistant hypertension, coronary artery disease

Апстракт

Резистентната хипертензија е присутна кај околу 30% од популацијата со хипертензија, при тоа потребни се најмалку четири антихипертензивни лекови за нејзино лекување и е асоцирана со кардиоваскуларни настани. Резистентната хипертензија често се јавува како коморбидитет со коронарната артериска болест, така што квантификацијата на вкупниот кардиоваскуларен ризик, најподобен е SCORE системот, е битна за проценка на ризикот и спроведување на терапијата за намалување на истиот.
Во оваа студија ги презентираме клиничките наоди на 66-годишна жена со резистентна хипертензија и коронарна артериска болест, нејзиното болничко лекување и препораките за домашно лекување по отпуштањето. Понатаму во дискусијата се наведени скорешните упатства и алгоритми за дијагноза и третман.
Како заклучок: хипертензијата е најчест ризик фактор кај пациентите со коронарна артериска болест и лекувањето на истата, особено резистентната хипертензија, е еден од најважните фактори за намалување на преваленцата на коронарната артериска болест, како и степенот на несакани кардиоваскуларни настани кај пациенти со постоечка коронарна артериска болест.

Клучни зборови: резистентна хипертензија, коронарна артериска болест

Introduction

Hypertension (HT) affects one third of the world population. Resistant hypertension (Res-HT) is a challenging clinical problem present in around 30% of hypertension population and is associated with cardiovascular (CV) events. Patients with Res-HT have 1.2-3-fold increased CV risk compared to hypertension population with controlled HT (treatment responsive hypertension) [1,2]. However, data regarding the impact of Res-HT on CV events in coronary artery disease (CAD) patients are insufficient.

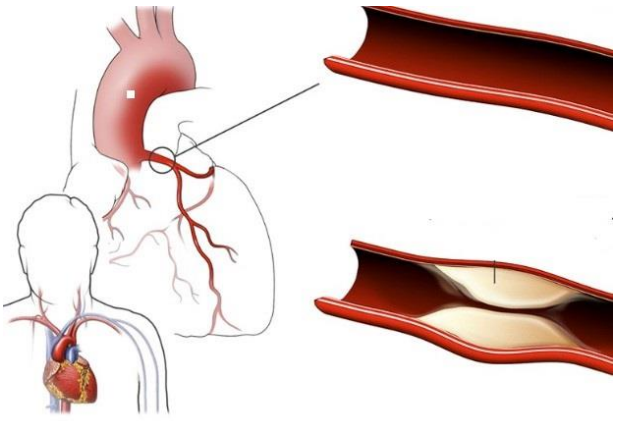

Fig. 1. Difference between a healthy coronary artery and CAD

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Coronary artery disease is a heart disease that affects larger coronary arteries which cannot deliver enough oxygen-rich blood to the heart (Figure 1). The causes of CAD are atherosclerosis and arteriosclerosis.

Resistant hypertension requires at least 4 antihypertensive blood pressure (BP) drugs for BP control.

Table 1. Classification of blood pressure and hypertension grade

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

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Aantihypertensive therapy for regulation of hypertension is required, but also habits and lifestyle changes are necessary. That includes:

1. Reduction of salt intake under 5 gr per day;
2. Increased intake of fruits and vegetables;
3. Maintenance of BMI between 20-25 kg/m^2;
4. Keeping waist circumference for women under 80 cm and for men under 94 cm;
5. Practicing daily physical activity for 30 minutes;
6. Reducing alcohol intake and complete cessation of smoking.

Besides HT, humans may have concomitant diseases like diabetes and hypertension, hypertension and chronic kidney disease, CAD and/or CVD and hypertension. Their interference creates circulus vitiosus and causes difficulty in HT control. Table 2 presents HT with concomitant diseases and their systolic/diastolic BP threshold under antihypertensive treatment.

Table 2. Blood pressure levels, concomitant disease - antihypertensive treatment

Age group	Office SBP treatment threshold (mmHg)					Office DBP treatment threshold (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18 - 65 years	≥140	≥140	≥140	≥140[a]	≥140[a]	≥90
65 - 79 years	≥140	≥140	≥140	≥140[a]	≥140[a]	≥90
≥80 years	≥160	≥160	≥160	≥160	≥160	≥90
Office DBP treatment threshold (mmHg)	≥90	≥90	≥90	≥90	≥90	

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With an aim to adjust/harmonize antihypertensive therapy worldwide, experts have given recommendations and antihypertensive therapy guidelines as follows:

1. Two antihypertensive drugs are recommended as an antihypertensive therapy by starting preferably one tablet with two active substances (for example ACE/ARA with diuretic or ACE/ARA + calcium antagonist),
2. Target values for BP: under 140/90 mmHg or as close as possible to 130/80 mmHg,
3. At high normal blood pressure 130-139/85-89 mmHg, antihypertensive therapy will be started at those who have increased cardiovascular risk or established CAD.

Assessment of hypertension and cardiovascular risk is necessary for timely initiation of appropriate therapy to prevent additional complications. So, quantification of total CV risk is important for risk stratification of hypertensive patients in order to see if statin therapy or antiplatelet therapy is necessary to reduce CV risk. CV

risk assessment is best done with the SCORE system, especially in patients with hypertension and confirmed CAD, diabetes, renal disease or elevated blood cholesterol level. Correlation between high blood pressure and cardiovascular and renal events is continuous, hence the need to distinguish normal blood pressure from hypertension.

Hypertension is often associated with other risk factors such as dyslipidemia and glucose intolerance, which on the other hand give a multiplying effect in the development of coronary artery disease.

Table 3. Classification of hypertension according to BP level, presence of BP risk factors, target organ damage and comorbidities

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

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Case report

The patient was a 66-year-old woman, who required a cardiology consultation for her frequent headaches and high unregulated blood pressure and chest pain. She had frequent attacks of headache and frequent outpatient internist and cardiologist consultations due to high and unregulated blood pressure levels. She had grade 3 hypertension, diabetes type 2 that has lasted for 10 years, and hyperlipidemia. Chronic kidney disease was discovered 5 years ago as a result of nephrolithiasis. She has been smoking for 20 years. She denied diseases of interest in the family history and food and drug allergy.

The patient was admitted to the hospital in a serious general condition with significantly high blood pressure (250/120 mm/Hg). Because she had signs of left heart failure with signs of incipient heart failure, she was admitted in the intensive care unit. During hospital stay, she was treated with intensive diuretic therapy, therapy with nitro-medications, calcium antagonists and ACE inhibitors.

After stabilization, she was transferred to the department unit for further investigation and additional therapy.

Upon further hospital examinations, ECG presented sinus rhythm with a heart rate of 78/min, biphasic T waves in D2 and aVL. System status was with normal function.

From the laboratory tests: glycemia 13.5 mmol/l, HgA1c 10.4%, triglycerides 5.15 mmol/l, total cholesterol 6.0 mmol/l, LDL 2.5 mmol/l, HDL 0.9 mmol/l. Elevated levels of creatinine and urea in serum were noted (creatinine 444. 410..456 μmol/L and urea 19. 4..20. 2..21.6 mmol/L). Holter blood pressure monitoring was performed with a finding of a high unregulated day-night blood pressure variations and echocardiographic findings presented a regular dimension of the LV with preserved EF and hypokinesia based on the lower wall. Carotid Doppler findings were with normal flow velocities, but thickened BMI and 50% stenosis in ACI lat. dexter were observed. Peripheral Doppler presented grade 1 of circulatory insufficiency in the legs and diabetic angioneuropathy. When coronarography was performed, two-vessel coronary artery disease (mLAD 70%, mRCA 85%) was found and percutaneous coronary intervention (PCI/RCA) was made. Ophthalmological examination presented grade 2 of hypertonic with non-proliferative diabetic retinopathy.

A nephrology specialist was consultant who gave advice on hydration and a proposal for further therapy.

During the hospital stay, an antihypertensive treatment was initiated upon the newest guidelines (Figure 2 and 3).

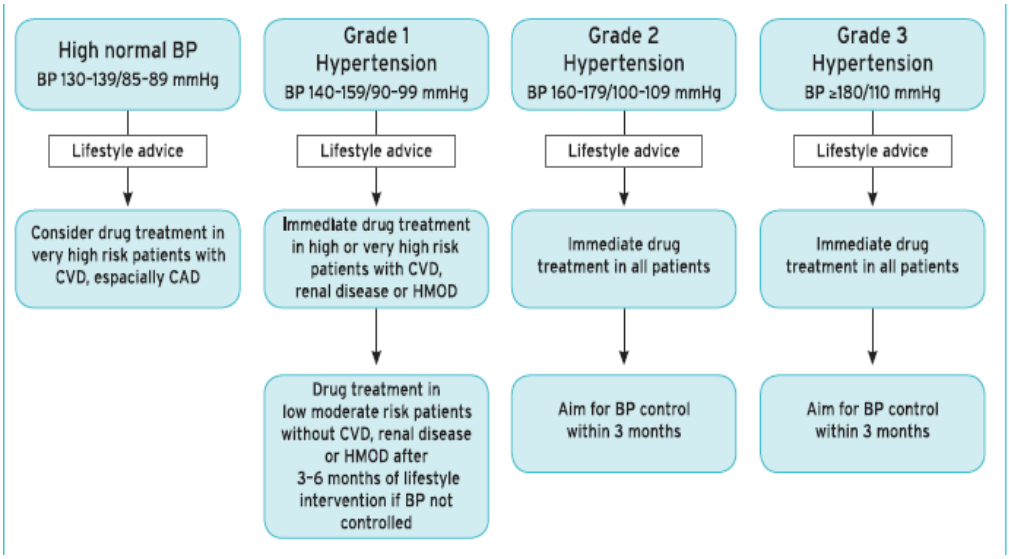

Fig. 2. Algorithm for initiation of antihypertensive treatment depending on BP level
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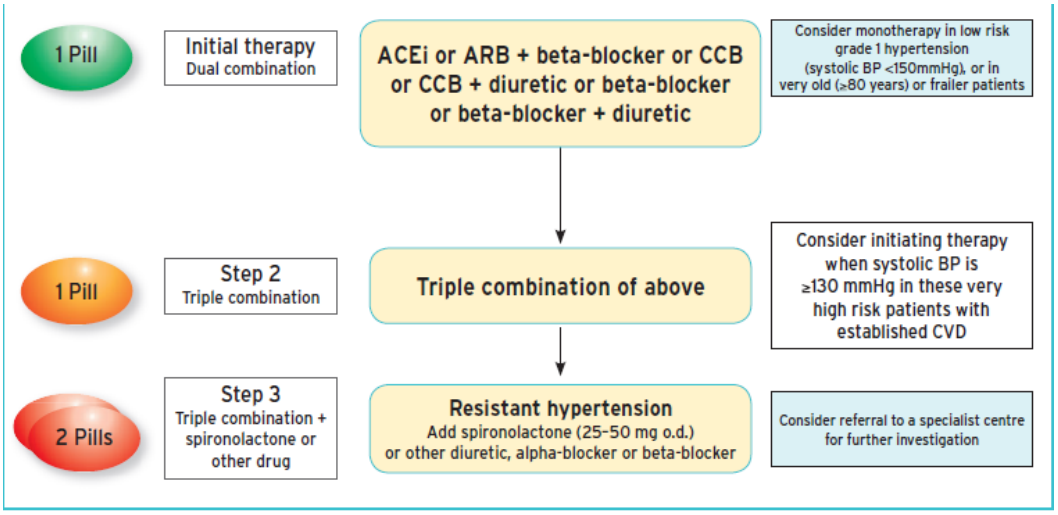

Fig. 3. Drug treatment in hypertension and CAD
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On the day of hospital discharge, antihypertensive, antiaggregation and antilipemic therapy was prescribed (Tabl. Aspirin a 100 mg 1x1, Tabl. Clopidogrel a 75 mg 1x1, Tabl. Rosuvastatin 40 mg 1x1, Tabl. Massido a 5 mg 1x1, Tabl. Relika 4/1.25 mg 1x1, Tabl. Spirinolactone a 25 mg 1x1 and Tabl. Prazosin a 2 mg 1x1) and a recommendation for a hygienic-dietary regimen; a home blood pressure diary and regular ambulatory monitoring was given.

Discussion

Hypertension is defined as resistant if the treatment strategy fails to regulate blood pressure (for systolic <140 mm/Hg, diastolic <90 mm/Hg). Various studies report a prevalence of resistant hypertension of 5-30%. Res-HT should be distinguished from pseudo-resistant hypertension. Poor adherence to prescribed medications, white-coat hypertension, brachial artery calcification are characteristics of pseudo-resistant hypertension.
Other conditions that contribute to unsatisfactory BP level control are: increased intake of salt and alcohol, higher body weight, taking cocaine and anabolics, obstructive sleep apnea.
For diagnostic approach in a patient with resistant hypertension it is important to recognize characterristics (symptoms and signs) of patients with Res-HTA and causes of secondary resistant hypertension (Table 4).

Table 4. Resistant hypertension characteristics, secondary causes and contributing factors

Table 24 Resistant hypertension characteristics, secondary causes, and contributing factors (adapted from reference[385])

Characteristics of patients with resistant hypertension	Causes of secondary resistant hypertension	Drugs and substances that may cause raised BP
Demographics • Older age (especially >75 years) • Obesity • More common in black people • Excess dietary sodium intake • High baseline BP and chronicity of uncontrolled hypertension	**More common causes** • Primary hyperaldosteronism • Atherosclerotic renovascular disease • Sleep apnoea • CKD	**Prescribed drugs** • Oral contraceptives • Sympathomimetic agents (e.g. decongestants in proprietary cold remedies) • Non-steroidal anti-inflammatory drugs • Cyclosporin • Erythropoietin • Steroids (e.g. prednisolone and hydrocortisone) • Some cancer therapies
Concomitant disease • HMOD: LVH and/or CKD • Diabetes • Atherosclerotic vascular disease • Aortic stiffening and isolated systolic hypertension	**Uncommon causes** • Phaeochromocytoma • Fibromuscular dysplasia • Aortic coarctation • Cushing's disease • Hyperparathyroidism	**Non-prescription drugs** • Recreational drugs (e.g. cocaine, amphetamines, and anabolic steroids) • Excessive liquorice ingestion • Herbal remedies (e.g. ephedra and ma huang)

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Resistant hypertension

Recommendations	Class[a]	Level[b]
It is recommended that hypertension be defined as resistant to treatment (i.e. resistant hypertension) when: • Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an ACE inhibitor or an ARB with a CCB and a thiazide/thiazide-type diuretic), fails to lower clinic SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively; and • The inadequate control of BP has been confirmed by ABPM or HBPM; and • After exclusion of various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension.	I	C
Recommended treatment of resistant hypertension is: • Reinforcement of lifestyle measures, especially sodium restriction.[395] • Addition of low-dose spironolactone[c] to existing treatment;[310,392,394] • Or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone,[c] amiloride,[c] a higher-dose thiazide/thiazide-like diuretic, or a loop diuretic;[d 357] • Or the addition of bisoprolol or doxazosin.[310]	I	B

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Fig. 4. Treatment of resistant hypertension

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It is an interesting finding that β-blockers have proclivity to increase the risk of developing Res-HT, probably due to the suppression of melatonin synthesis in the pineal gland, which as a final result lead to an increased activity of the sympathetic nervous system [3-5].

Confirmation that Res-HT increases the risk of major CV events and all-cause mortality is found in S. Smith *et al.* study from 2014 [6] as well as in two other studies [1,2] in which Res-HT was associated with a poorer prognosis than nonresistant hypertension. These studies found an increased risk of adverse outcomes

and all-cause mortality as well as CV mortality in patients with Res-HT. Additionally, the Smith's study confirmed that a similar increased risk was associated with Res-HT in patients with concomitant CAD, although event rates were considerably greater in patients with CAD than in those without CAD. However, the pathophysiology of Res-HT increased CV risk is unknown and the assumption is that increased renin-angiotensin system stimulation and aldosterone production leads to increased arterial stiffness and atherosclerotic disease, i.e., increased CV risk [7]. Also, it has been observed that if a higher dose as well as a higher number of antihypertensive drugs are required (regardless of whether it leads to control of Res-HT or not) the CV risk increases [7], so the use of a larger number of antihypertensive agents may not fully mitigate the long-term risks of elevated BP [8], although this is unlikely according to other studies [6]. In agreement with these findings is VALUE study, where patients who received combined antihypertensive therapy to control non-resistant hypertension had a significantly higher risk of CV death compared to those who received only monotherapy [8]. These suggest that Res-HT is an important prognostic factor, and even more valuable than BP control.

Conclusion

Hypertension is the most common risk factor in patients with coronary vascular disease and its early diagnosis is mandatory because the population of patients with HT and CAD is growing worldwide.
Regulation of elevated BP, especially in the resistant form of hypertension, is one of the most important factors for reducing the prevalence of CAD as well as the degree of major adverse cardiovascular events in patients with existing CAD. Res-HT alone portends an increased risk of major CV events and death. Further clinical research is necessary, especially in patients with diabetes, CKD and cardiovascular disease, who as a comorbidity have Res-HT for determination of strategies for its CIE reduction and their CIE complication reductions as well.

Conflict of interest statement. None declared.

Reference

1. Daugherty SL, Powers JD, Magid DJ, *et al*. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012; 125: 1635-1642.
2. Kumbhani DJ, Steg PG, Cannon CP, *et al*. Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis. *Eur Heart J* 2013; 34:1204-1214.
3. Paulis L, Simko F. Blood pressure modulation and cardiovascular protection by melatonin: potential mechanisms behind. *Physiol Res* 2007; 56: 671-684.
4. Kario K. Are melatonin and its receptor agonist specific antihypertensive modulators of resistant hypertension caused by disrupted circadian rhythm? *J Am Soc Hypertens* 2011; 5: 354-358.
5. Scheer FA, Van Montfrans GA, van Someren EJ, *et al*. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. *Hypertension* 2004; 43: 192-197.
6. Smith S, Gong Y, Handberg E, *et al*. Predictors and outcomes of resistant hypertension among patients with coronary artery disease and hypertension. *J Hypertens* 2014; 32(3): 635-643.
7. Smith SM. Epidemiology, prognosis, and treatment of resistant hypertension. *Pharmacotherapy* 2013; 33: 1071-1086,
8. Weber MA, Julius S, Kjeldsen SE, *et al*. Cardiovascular outcomes in hypertensive patients: comparing single-agent therapy with combination therapy. *J Hypertens* 2012; 30: 2213-2222.