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Review

Resistant Hypertension and Cardiorenovascular Risk

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Abstract

Studies have documented independent contribution of sympathetic activation to the cardiovascular disease continuum. Hypertension is one of the leading modifiable factors. Most if not all the benefit of antihypertensive treatment depends on blood pressure lowering, regardless how it is obtained. Resistant hypertension is defined as blood pressure that remains uncontrolled in spite of the concurrent use of three antihypertensive drugs of different classes. Ideally, one of the three drugs should be a diuretic, and all drugs should be prescribed at optimal dose amounts.

Poor adherence to antihypertensive therapy, undiscovered secondary causes (e.g. obstructive sleep apnea, primary aldosteronism, renal artery stenosis), and lifestyle factors (e.g. obesity, excessive sodium intake, heavy alcohol intake, various drug interactions) are the most common causes of resistant hypertension.

Cardio(reno)vascular morbidity and mortality are significantly higher in resistant hypertensive than in general hypertensive population, as such patients are typically presented with a long-standing history of poorly controlled hypertension. Early diagnosis and treatment is needed to avoid further end-organ damage to prevent cardiorenovascular remodeling.

Treatment strategy includes lifestyle changes, adding a mineralocorticoid receptor antagonist, treatment adherence in cardiovascular prevention and, in case of failure to control blood pressure, renal sympathetic denervation or baroreceptor activation therapy. The comparative outcomes in resistant hypertension deserve better understanding. In this review, the most current approaches to resistant hypertension and cardiovascular risk based on the available literature evidence will be discussed.

Keywords: resistant hypertension, cardiorenovascular risk

Introduction

Despite numerous treatment methods, a significant number of patients does not achieve optimal blood pressure levels. Resistant hypertension (RH) is diagnosed when treatment strategy including lifestyle changes and use of three antihypertensive drugs (one of them being a diuretic) at recommended doses fails to lower systolic blood pressure (SBP) and diastolic blood pressure (SBP) values to <140 and <90 mmHg (<140/85 mmHg for diabetic patients), or when patients use four or more antihypertensive drugs regardless of blood pressure control [1]. The prevalence of RH in general hypertensive population is 10-15% [2,3]. RH can be real or apparent (pseudoresistant). The most common causes of pseudoresistance are:

1) poor adherence to antihypertensive therapy;
2) white-coat effect;
3) inaccurate measurement of blood pressure;
4) pseudohypertension, i.e. arterial stiffening caused by extensive calcifications which prevents occlusion of the brachial artery; it is more common in elderly patients [4].

Poor adherence to antihypertensive therapy is the most important cause of unsuccessful blood pressure control. Retrospective analyses show that approximately 40% of patients will not continue their antihypertensive medications during the first year after diagnosing RH. During 5-10 years of follow-up, those numbers reach 60% [5]. Inaccurate blood pressure measurement is not uncommon; it occurs when patients are not instructed to sit calmly and quietly, and when the cuff is too small [6]. Keeping that in mind, pseudoresistant hypertension should not be confused for real one in order to avoid unnecessary diagnostic procedures and treatments. Successful treatment involves the physician (correct pharmacological approach, reduce therapeutic inertia) and the patient (to regulary take medications that have been proven effective and well tolerated).

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We need diagnosis-based approach that takes into consideration not only a person's blood pressure but also the overall cardiovascular risk (CVD) [7].

Predictors of resistant hypertension

Studies of RH are limited by high cardiovascular (CV) risk in this population; comorbidities (e.g. diabetes, chronic kidney disease, obstructive sleep apnea) and their associated medical therapies which can be confounding factors; and the inability to include a large number of study participants [8]. However, studies show that BP is usually not regulated because of persistently elevated SBP [9]. In early adulthood, SBP is higher in men than in women, whereas after the age of 60, it is higher in women. DBP values also increase until the age of 55, and later steadily lower. Consequently, pulse pressure (the difference between SBP and DBP) increases. Other predicting factors are old age, obesity, and chronic kidney disease [9,10].

Etiology

RH has an extreme phenotype, so it would be reasonable to expect that genetic factors may play a great role. Although the genetic researches are limited, a certain number of genes has been associated with impaired response to antihypertensive treatment. However, environmental factors contribute to the development of RH, making it a multifactorial disease [4].
Lifestyle factors that are associated with RH are obesity (BMI>30 kg/m2), excessive dietary sodium intake, heavy alcohol intake, and use of drugs such as nonnarcotic analgesics, especially nonsteroidal antiinflammatory agents (NSAIDs) [4].
Secondary causes include unrecognized/untreated obstructive sleep apnea (OSA), primary aldosteronism, chronic parenchimal kidney disease, renal artery stenosis, and diabetes. Uncommon causes are pheochromocytoma, Cushing's disease, aortic coarctation, and intracranial tumors [8].

Diagnosis

To determine true hypertension, the French Society of Hypertension gave the following recommendations [11]:

1) To avoid poor blood pressure measurement, a standardized device and an appropriate cuff-size should be used;
2) White-coat effect should be eliminated by ambulatory (ABPM) or home (HBPM) blood pressure measurement. Thresholds for uncontrolled hypertension are: HBPM≥135/85 mmHg, 24-h ABPM ≥130/80 mmHg, day-time ABPM ≥135/85 mmHg, night-time ABPM ≥120/70 mmHg;
3) It is necessary to determine if the optimal triple-drug therapy is prescribed;
4) Poor patient compliance should be assessed using a questionnaire, urine drug analysis and pill-count;
5) It is suggested to search for factors that could influence treatment resistance (e.g. obesity, excessive dietary sodium intake, alcohol, drug interactions).

After true resistant hypertension is confirmed, evaluation should include identification of the underlying cause, and assessment of cardiovascular risk and end-organ damage [12]. While secondary causes are relatively rare in general hypertensive population, they are frequently found in RH. Medical history can be useful: loud snoring, daytime sleepiness and witnessed apnea indicate OSA; a history of peripheral or coronary atherosclerotic disease and worsening kidney funcion are suspicious for renal artery stenosis; labile hypertension followed by palpitations and diaphoresis indicate the possibility of pheochromocytoma. In physical examination, carotid, abdominal or femoral bruits indicate renal artey stenosis; moon facies, abdominal striae and central obesity suggest Cushing's disease; diminished femoral pulses and difference between arm and thigh blood pressures are suspicious for aortic coarctation or aortoiliac disease. Biochemical evaluation should include routine metabolic profile (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, albumin/creatinine ratio, eGFR), urine proteins, plasma aldosterone and renin so as their ratio can be calculated (high aldosterone/renin ratio indicates primary aldosteronism), metanephrine and normetanephrine in 24-hour urine, cortisol in 24-hour urine. Doppler of renal arteries, MR or MSCT angiography are recommended to assess the anatomy before RDN [12]. Lastly, screening for possible end-organ damage is extremely important [8].

Device therapies for resistant hypertension

In recent decades, the use of antihypertensive drugs has revolutionised the therapy of hypertension. Despite the available pharmacological inhibition of the sympathetic nervous system, about 50% of patients show suboptimal control and pharmacotherapy does not provide adequate effects in clinical practice. A hyperactivity of the sympathetic nervous system is a condition that confers a high cardiovascular risk in the patient [12,13]. New devices like Renal sympathetic denervation, Baroreceptor activation therapy and Continuous positive airway pressure were developed to interrupt the cardiovascular disease continuum, the leading cause of death globally.

Renal sympathetic denervation

Renal sympathetic denervation delivers energy to the renal nerves to help control blood pressure. Many observational studies have shown that RDN is a safe method of reducing office BP in patients with RH, with an additional positive effect on blood glucose metabo-

lism, obstructive sleep apnea and signs of hypertensive end-organ damage [12,14]. The reasons for the rapid introduction of RDN in the therapy of rHT were the reported high efficiency and safety of the procedure. The effectiveness was demonstrated in the studies Symplicity HTN-1 and HTN-2, and in the EnligHTN-1 Study (by using special RF ablation catheters). According to the results of different trials, including Symplicity HTN-3 (this study did not show differences in SBP reduction between treatment and control groups, but in the context of the study characteristics and the way it was conducted, there are several concerns about inexperienced doctors in the field of RDN, the study population and the medical treatment), RDN is safe and procedure-related complications of catheter-based RDN were very rare [12].

Baroreceptor activation therapy

Baroreceptor activation therapy (BAT) or baropacing can be applied in patients with treatment resistant hypertension. When baroreceptors sense an icrease in carotid transmural pressure, they respond by inhibiting sympathetic and stimulating parasympathetic centres in the brainstem [15]. As a result, any increase in blood pressure (BP) will return to its initial level. Most studies on BAT took only office BP as criterion for efficacy but only one study in which the effect on 24-hour was assessed showed that BP had fallen by 8/5 mmHg afer 6 months of therapy which was statistically significant [15].

Continuous positive airway pressure

Nasal continuous positive airway pressure (CPAP) ventilation is considered the treatment for obstructive sleep apnea (OSA) of moderate to severe degree [16]. The effects of CPAP on BP levels have been shown to be variable, but in some subgroups of patients, those with severe OSA or/and with RH, more substantial effects of CPAP have been reported [16].

Discussion

Cardiovascular diseases were the leading cause of mortality in 2012, comprising 31% of all deaths and killing 17.5 million people. Hypertensive disease of the heart, blood vessels, brain and kidney is frequently found in patients with RH. RH is a consequence of different pathophysiologic processes (e.g. increased stimulation of renin-angiotensin system and aldosterone production, arterial stiffness, atherosclerotic disease) that are associated with high cardiovascular risk [8].

CV morbidity and mortality is noted in patients with both high and relatively low levels of blood pressure (110-115 mmHg SBP and 70-75 mmHg DBP). CV risk doubles with increase of 20 mmHg SBP and 10 mmHg DBP [7]. SBP is a better predictor than DBP after the age of 50, and it seems that in older patients pulse pressure plays a significant role; that is indicated by particularly high CV risk in patients with high SBP and normal or low levels of DBP [17]. Other risk factors that are usually related with RH have a synergistic effect in development and worsening of RH.

Studies have shown 47% higher risk of cardiovascular morbidity and mortality in RH patients [18,19]. Significant worsening of heart and blood vessel disease and higher mortality has been noted in subpopulations with preexistant ischemic heart disease [20]. Studies indicate a notably higher CV risk in patients with RH and diabetes or chronic kidney disease compared to general hypertensive population [21,22]. Compared with the non-RH population, the RH population had a greater prevalence of comorbid conditions including diabetes mellitus (DM, 48% vs. 30%), CKD (45% vs. 24%), ischemic heart disease (41% vs. 22%), cerebrovascular disease (16% vs. 9%; $P<0.001$ for all) [23]. Compared with controlled RH patients (cRH)-individuals with uncontrolled RH (uRH; 61.7%) were at a greater risk for cerebrovascular (CVA) and end-stage renal disease (ESRD). The risk of ESRD and CVA were 25% and 23% greater, respectively, in uRH compared with cRH, supporting the linkage between blood pressure and both outcomes [23].

Patients with diabetes and/or chronic kidney disease (CKD) have sympathetic nervous system hyperactivation that leads to fluid overload, aggravation of hypertension and further deterioration and loss of renal function, and it has been demonstrated that RDN is associated with stabile kidney function [12]. The most obvious explanation relating effect of stabile kidney function could be that after RDN treatment an increased renal blood flow will result in increase in GFR. Renal sympathetic denervation (RDN) produce multilevel inhibition of the sympathetic nervous system, and trigers additional positive metabolic effects [13,14].

The effectiveness of all therapeutic approaches should be tested in diverse settings of uRH. Carefully designed studies (some ongoing, such as SPYRAL HTN OFF and ON-MED) will provide the evidence that RDN is also an efficacious therapy [14]. Further meta analysis will evaluate the importance of new devices.

Conclusions

It is widely accepted that hypertension is associated with a number of other CV risk factors (metabolic syndrome, endothelial dysfunction, arterial stiffness or kidney disease) that makes it a part of a multifactorial process in disease development. Poor adherence is a major cause of lack of blood pressure control and it can be misleading in further diagnostics and treatment with detection of drugs in blood and/or urine. Among chronic kidney disease (CKD) patients, those with RH have been reported to experience a two-fold greater

risk for both cardiovascular events and ESRD, compared with those without resistant hypertension.
RH population may benefit from more individualized care rather than broad, general recommendations

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Reference

1. Vongpatanasin W. Resistant hypertension: a review of diagnosis and management. *JAMA* 2014; 311: 2216-2224.
2. Egan BM, Zhao Y, Axon RN, *et al*. Uncontrolled and Apparent Treatment Resistant Hypertension in the U.S. 1988–2008. *Circulation* 2011; 124(9): 1046-1058. doi: 10.1161/CIRCULATIONAHA.111.030189.
3. Sim JJ, Bhandari SK, Shi J, *et al.* Characteristics of Resistant Hypertension in a Large Ethnically Diverse Hypertension Population of an Integrated Health System. *Mayo Clinic Proceedings* 2013; 88(10): 1099-1107.
4. Prkacin I, Balenovic D, Jurina A, *et al*. Underestimated frequency of resistant hypertension in predialysis nondiabetic patients. *Acta Med Croatica* 2012; 66 (3): 229-233.
5. Pimenta E. Update on Diagnosis and Treatment of Resistant Hypertension. *Iran J Kidney Dis* 2011; 5(4): 215-227.
6. Bilo G, Sala O, Perego C, *et al*. Impact of cuff positioning on blood pressure measurement accurancy: may a special designed cuff make a difference? *Hypertension Research* 2017; 40(6): 573-580. doi: 10.1038/hr.2016.184.
7. Whelton PK, Reboussin DM, Fine LJ. Comparing SPRINT and the HOPE-3 blood pressure trial. *JAMA Cardiol* 2016; 1(8): 857-858. DOI:10.1001/jamacardio.2016.2051.
8. 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): e510-e526.
9. Gupta AK, Nasothimiou EG, Chang CL, *et al.* Baseline predictors of resistant hypertension in the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT): a risk score to identify those at high-risk. *Hypertension* 2011; 29(10): 2004-2013. doi: 10.1097/HJH.0b013e32834a8a42.
10. Prkacin I, Ozvald I, Cavric G, *et al*. Importance of urinary NGAL, serum creatinine standardization and estimated glomerular filtration rate in resistant hypertension. *Coll Antropol* 2013; 37 (3): 821-825.
11. Denolle T, Chamontin B, Doll G, *et.al.* Management of resistant hypertension: expert consensus statement from the French Society of Hypertension, an affiliate of the French Society of Cardiology. *J Hum Hypertens* 2016. doi: 10.1038/jhh.2015.122.
12. Prkacin I, Vrhovec B, Legovic A, *et.al*. Renal denervation and resistant hypertension: back to the future. *Acta Med Croatica* 2016; 70(2): 41-45.
13. Prkacin I, Balenovic D, Djermanovic-Dobrota V, *et al*. Resistant hypertension and Chronotherapy. *Mater Sociomed* 2015; 27(2): 118-121.
14. Kandzari DE, Kario K, Mahfoud F, *et al*. The SPYRAL HTN Global Clinical Trial Program: Rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications. *Am Heart J* 2016; 171: 82-91.
15. Walbach M, Lehnig LY, Schroer C, *et al*. Effect of baroreflex activation therapy on ambulatory blood pressure in patients with resistan hypertension. *Hypertension* 2016; 67: 701-709.
16. Feldstein CA. Blood pressure effects of CPAP in nonresistant and resistant hypertension associated with OSA. A systematic review of randomized clinical trials. *Clin Exp Hypertens* 2016; 38: 337-346.
17. Vishram JK, Borglykke A, Andreasen AH, *et al*. Impact of Age on the Importance of Systolic and Diastolic Blood Pressures for Stroke Risk: The MOnica, Risk, Genetics, Archiving and Monograph (MORGAM) Project. *Hypertension* 2012; 60: 1117-1123.
18. Daugherty SL, Powers JD, Magid DJ, *et al*. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012; 125(13): 1635-1642.
19. Bangalore S, Fayyad R, Laskey R, *et al*. Prevalence, predictors, and outcomes in treatment-resistant hypertension in patients with coronary disease. *Am J of Med* 2014; 127(1): 71-81.
20. Smith SM, Gong Y, Handberg E, *et al.* Predictors and outcomes of resistant hypertension among patients with coronary artery disease and hypertension. *Hypertension* 2014; 32(3): 635-643.
21. De Nicola L, Gabbai FB, Agarwal R, *et al.* Prevalence and prognostic role of resistant hypertension in chronic kidney disease patients. *J Am College of Cardiology* 2013; 61(24): 2461-2467.
22. American Diabetes Association. Cardiovascular disease and risk management. Sec 8. In Standards of Medical Care in Diabetes. *Diabetes Care* 2016; 39(1): S60-S71.
23. Sim JJ, Bhandari SK, *Shi* J, *et al*. Comparative Risk of Renal, Cardiovascular, and Mortality Outcomes in Controlled, Uncontrolled Resistant, and Nonresistant Hypertension. *Kidney Int* 2015; 88(3): 622-632.