DOI: 10.5455/msm.2015.27.118-121
Received: 15 March 2015; Accepted: 05 April 2015
Published online: 05/04/2015 Published print:04/2015

REVIEW Mater Sociomed. 2015 Apr; 27(2): 118-121

Resistant Hypertension and Chronotherapy

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ABSTRACT

Resistant hypertension is defined as blood pressure that remains above 140/90 mmHg in spite of the continuous use of three antihypertensive agents in optimal dose, including diuretic, and lifestyle changes. According to data from United States of America and Europe, the prevalence ranges from 10 up to 30% in patients with hypertension. Numerous biological and lifestyle factors can contribute to the development of resistant hypertension: medications, volume overload, obesity, diabetes mellitus, older age, renal parenchymal and renovascular disease, primary aldosteronism, obstructive sleep apnea, pheochormocytoma, Cushing's syndrome, thyroid diseases, aortic coarctation. For diagnosing patient's history is important, assessing compliance, regular blood pressure measurement, physical examination, biochemical evaluation and noninvasive imaging. The evaluation including 24h ambulatory monitoring of blood pressure (ABPM) in the identification of "non-dipper" hypertension. Non-dipper has particular importance and the prevalence of abnormally high sleep blood pressure is very often in chronic kidney patients. Therapeutic restoration of normal physiologic blood pressure reduction during night-time sleep (circadial variation) is the most significant independent predictor of decreased risk and the basis for the chronotherapy. The resistant hypertension treatment is achieved with nonpharmacological and pharmacological approach, treating secondary hypertension causes and invasive procedures.

Keywords: resistant hypertension, circadian variation, chronotherapy.

1. INTRODUCTION

According to European society of cardiology guidelines, hypertension is usually defined as resistant or refractory to treatment when a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs (including a diuretic) in adequate doses has failed to lower systolic (SPB) and diastolic blood pressure (DBP) to goal (<140/90 mmHg) (1). According to American criteria patients with refractory (resistant) hypertension could be considered as patients who have at least four antihypertensive drug independently from BP levels. Park and Campese add more to definition for patients with diabetes or renal failure (defined as serum creatinine level > 1,5 mg/dL or 133 μmol/L and/or proteinuria > 300 mg/24h) as failure to achieve BP level up to 135/75 mmHg with the above mentioned criteria (2). Some authors include inability to lower SBP below 160 mmHg in patients with isolated systolic hypertension. Resistant hypertension is not a synonym for uncontrolled hypertension. The latter includes all hypertensive patients lacking BP control under therapy, those who underwent inadequate therapeutic regimen, those with poor compliance, and those with undiscovered secondary hypertension, as well as those who are really resistant to treatment. Although the definition for resistant hypertension is arbitrary in regard to the number of needed antihypertensive drugs, the concept of resistant hypertension is directed towards recognizing the patients that are under high risk of having reversible causes for hypertension, and/or patients who will, because of permanently high level BP, use special diagnostic and therapeutic considerations (3).

Resistant hypertension should be discerned from pseudoresistance. Pseudoresistance is defined as lack of control over BP levels caused by inappropriate BP measurement, inappropriate drug choice/dosage, lack of compliance to prescribed therapy, or by white-coat effect. White-coat hypertension is to be considered in patients who have repeatedly high BP ambulatory measured without proof of target organs damage. White-coat hypertension has better prognosis than resistant hypertension, but has a higher cardiovascular risk than in persons with normal BP levels (2). Pseudoresistance is often misdiagnosed as resistant hypertension (4).

The prevalence of resistant hypertension is unknown: epidemiological researches on resistant hypertension are missing. The data of frequency can be taken out from observational and big controlled clinical studies in which many participants partaken. For example, in ALLHAT study after five year follow-up, 34% of participants had uncontrolled arterial hypertension, and 27% had resistant hypertension (5). At the end of the study, 8% of participants were prescribed four or more drugs, while 15% of participants were classified in resistant hypertension group (5).

In VALUE study 15% of patients received three or more drugs, and 61% of them retained high BP (6). Based on specified data from mentioned studies, the prevalence in United States of America (USA) and Europe is between 10 to 30% among patients with hypertension. According to Persell's results, 12.8% of antihypertensive drug-treated adults meet the operational definition of resistant hypertension (7). If we compare the resistant hypertension frequency in GP's office where prevalence is around 5% with nephrologists' office where the prevalence (because of patients selection) is up to 50%, we can see how hard it is to estimate the exact number of patients with resistant hypertension (8). In opposition to USA and Europe data, for the time being it is not possible to assess the prevalence of resistant hypertension in Croatia due to lack of research on the subject.

According to Sarafidis and Bakris (3) many biological and life-style factors can contribute to the development of resistant hypertension:

Drugs induced: Nonsteroidal anti-inflammatory drugs (including cyclo-oxygenase-2 inhibitors), sympathomimetics (decongestants, anorectics), cocaine, amphetamines, other illicit drugs, oral contraceptive hormones, adrenal steroid hormones, erythropoietin, cyclosporine and tacrolimus, licorice (included in some chewing tobacco), over-the-counter dietary and herbal supplements (e.g., ginseng, yohimbine, ma huang, bitter orange)

Excess alcohol intake

Volume overload: Excess sodium intake, volume retention from kidney disease, Inadequate diuretic therapy

Associated conditions: Obesity, diabetes mellitus, older age

Identifiable causes of hypertension: Renal parenchymal disease, renovascular disease, primary aldosteronism, obstructive sleep apnea, pheochromocytoma, Cushing's syndrome, thyroid diseases, aortic coarctation, intracranial tumors

Renal physiology contributes to circadial variability of blood pressure levels. The time-related profile of blood pressure levels shows a morning increase, a deeper descent during nocturnal rest: 10-20% drop during the night in healthy subject. Patients with secondary hypertension very often display abnormal circadian blood pressure profile, leading to the "non-dipper" pattern, requiring different ingestion-time dependent strategies for therapy of hypertension medications (9).

According to article published by Calhoun et al. 2008 in Circulation, the evaluation of patients with resistant hypertension should, be directed toward confirming true treatment resistance; identification of causes contributing to treatment resistance, including secondary causes of hypertension; and documentation of target-organ damage (10). Accurate assessment of treatment adherence and use of good BP measurement technique is required to exclude pseudoresistance. Target-organ damage such as retinopathy, chronic kidney disease, and left ventricle hypertrophy supports a diagnosis of poorly controlled. Calhoun et al. suggest following algorithms for establishing resistant hypertension diagnosis (10):

The **medical history** should document duration, severity, and progression of the hypertension; treatment adherence; response to prior medications, including adverse events; current medication use, including herbal and over-the-counter medications; and symptoms of possible secondary causes of hypertension. Daytime sleepiness, loud snoring, and witnessed apnea are suspicious for sleep apnea. A history of peripheral or coronary atherosclerotic disease increases the likelihood of renal artery stenosis. Labile hypertension, in association with palpitations and/or diaphoresis, suggests the possibility of pheochromocytoma.

Assessing compliance. Ultimately, adherence in a clinical setting can only be known by patient self-report. Patients should be specifically asked how successful they are in taking all of their prescribed doses, including discussion of adverse effects, out-of-pocket costs, and dosing inconvenience, all of which can limit adherence. Family members will often provide more objective assessments of a patient's adherence, but such input should generally be solicited in the presence of the patient. Direct observation of therapy is the most accurate method but is burdensome to both patients and providers and impractical for chronic diseases. Blood or urine measurements of drug levels or biologic markers are expensive and may falsely suggest adherence in patients who take their medications only around the time of their clinic visit—white coat adherence. Self-reporting and pillbox counting are feasible but easily subject to patient manipulation. They also state that gold standard in assessing adherence and can provide daily information on patient pillbox access with timing intervals. The Medication Event Monitoring System (MEMS) records each time and date that the pillbox is opened and electronically stores this information, which can later be accessed by computer. These devices are the most reliable system for monitoring adherence and have been shown to improve adherence in hypertensive patients : 30% of patients with a prior diagnosis of resistant hypertension normalized their blood pressure by undergoing electronic adherence monitoring, and an additional 20% were identified as non-adhering to the medication regimen.

Blood pressure monitoring

Use of adequate BP measurement technique is essential to the accurate diagnosis of resistant hypertension, including having the patient sit quietly in a chair with his or her back supported for 5 minutes before taking the measurement; use of the correct cuff size with the air bladder encircling at least 80% of the arm (the adult large cuff for the majority of patients); and supporting the arm at heart level during the cuff measurement. A minimum of 2 readings should be taken at intervals of at least 1 minute and the average of those readings should be taken to represent the patient's BP. The BP should be measured carefully on both arms and the arm with the higher pressures generally should be used to make future measurements (10).

Physical examination

A fundoscopic examination should document the presence and severity of retinopathy. The presence of carotid, abdominal, or femoral bruits increases the possibility that renal artery stenosis exists. Diminished femoral pulses and/or a discrepancy between arm and thigh BPs suggest aortic coarctation or significant aortoiliac disease. Cushing's disease is suggested by abdominal striae, particularly if pigmented; moon facies; or prominent interscapular fat deposition (10).

Ambulatory blood pressure monitoring

Documentation of a significant white-coat effect requires reliable assessment of out-of-office blood pressure values. This is accomplished most objectively with the use of 24-hour ambulatory blood pressure monitoring (ABPM) (10). ABPM has greater diagnostic value and is useful in assessing patients for white coat hypertension, episodic hypertension, autonomic dysfunction, and masked hypertension and will determine whether

patients have the appropriate nocturnal dip in blood pressure of 10%–20%. Patients without the appropriate nocturnal dip have increased cardiovascular risk, so the evaluation of resistant hypertension including 24h ambulatory monitoring of blood pressure in the identification of "non-dipper" hypertension (2,9). "Non-dipper "has particular importance and the prevalence of abnormally high asleep blood pressure is very often in chronic kidney disease patients. Therapeutic restoration of normal physiologic blood pressure reduction during night-time sleep is the most significant independent predictor of decreased cardiovascular risk in patients with chronic kidney disease (CKD)(9).

Biochemical Evaluation

Biochemical evaluation of the treatment-resistant hypertensive should include a routine metabolic profile (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, and creatinine); urinalysis; and a paired, morning plasma aldosterone and plasma renin or plasma renin activity to screen for primary aldosteronism. Even in the setting of ongoing antihypertensive treatment (excluding potassium sparing diuretics, particularly aldosterone antagonists), the aldosterone/renin ratio is an effective screening test for primary aldosteronism, having a high negative predictive value. A high ratio has a low specificity for primary aldosteronism, likely reflecting the common occurrence of low-renin hypertension in patients with resistant hypertension. A 24-hour urine collected during ingestion of the patient's normal diet can be helpful in estimating dietary sodium and potassium intake, calculating creatinine clearance, and measuring aldosterone excretion. Measurement of 24-hour urinary metanephrines or plasma metanephrines is an effective screen for patients in whom pheochomocytoma is suspected (10). In opposite to Calhoun et al statements, according to Park and Capese , an aldosterone-to-plasma renin activity ratio of greater than 20:1 is usually considered suggestive of primary aldosteronism, with sensitivity and specificity of 89% and 71%, respectively (2).

Noninvasive Imaging

Imaging for renal artery stenosis should be reserved for patients in whom there is an increased level of suspicion. This would include young patients, particularly women, whose presentation suggests the presence of fibromuscular dysplasia and older patients at increased risk of atherosclerotic disease. The preferred imaging modality will vary by institution, depending on the level of training and experience. For patients with CKD, modalities that do not involve iodinated contrast may be preferred over computed tomography (CT) angiography. Diagnostic renal arteriograms in the absence of suspicious noninvasive imaging are not recommended. Likewise, due to poor specificity, abdominal CT imaging is not recommended to screen for adrenal adenomas in the absence of biochemical confirmation of hormonally active tumors (hyperaldosteronism, pheochromocytoma, Cushing's syndrome) (8). Oppose to Calhoun et al., Park and Campese state that in patients with a high ratio and hypokalemia, further workup can be performed with a sodium loading test; patients with an abnormal response can then undergo adrenal imaging with computed tomography or magnetic resonance imaging. Along with diagnostic approach suggested by Calhoun et al., Park and Campese complement the algorithm stated above with a few diagnostic procedures. They state that An ECG should be performed in all patients with resistant hypertension. Left ventricular hypertrophy determined by Cornell voltage on ECG is associated with resistant hypertension, and ECG strain pattern (S in V_3 + R in aVL > 28mm for men; and S in V_3 + R in aVL > 20mm for women) is independently associated with increased left ventricular wall thickness and other adverse factors in patients with resistant hypertension. Additionally, all patients with resistant hypertension should have a glomerular filtration rate calculated by the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to better discern the level of kidney function (12**).** Renovascular disease is highly prevalent in the elderly population, but it may be difficult to determine whether the disease is indeed the cause of the resistant hypertension. Screening for renovascular disease may be performed with Doppler ultrasonography, magnetic resonance angiography, or angiotensin-converting enzyme inhibitor renography.

Treatment of resistant hypertension is predicated on identification and reversal of lifestyle factors contributing to treatment resistance; accurate diagnosis and appropriate treatment of secondary causes of hypertension; and use of effective multi-drug regimens. Potential measures that could contribute to welfare of the patients with resistant hypertension are:

- Non-pharmacological: Lifestyle changes (weight loss, regular exercise, ingestion of a high-fiber, low-fat, low-salt diet; and moderation of alcohol intake)
- Pharmacological: Compared with morning administration, dosing one or more antihypertensive medications at bedtime helps induce a normal circadian BP pattern and reduces the cardiovascular risk. In chronic kidney disease (CKD), the diagnosis of hypertension and treatment are based usually on daytime clinic blood pressure measurements. Evidence is that the asleep BP better predicts cardiovascular events than the awake or 24 h blood pressure mean. The therapeutic strategy should be preferred according ABPM (9,11). A small retrospective analysis assessing the safety of spironolactone (on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium-channel blockers, beta blockers and diuretics) in patients with resistant hypertension suggests that hyperkalemia occurs not infrequently and that further studies are needed to assess the safety of the drug in these difficult-to-treat patients (13).
- Treatment of secondary causes of hypertension (obstructive sleep apnea, renal artery stenosis ...)
- Invasive procedures: carotid sinus stimulation, renal denervation (10).

2. CONCLUSION

Hypertension has the largest prevalence of 30-45% of all cardiovascular risk factors. The achievement of blood pressure values below 140/90 mmHg is considered one of the main methods of achieving high long term patient quality of life. Nevertheless, a substantial number of patients do not achieve target blood pressure values in spite of taking at least three antihypertensive medications in adequate dosage of which one is a diuretic, so resistant hypertension is still unrecognized as a diagnosis and insufficiently researched. Because of diagnostic procedure complexity, both doctor and patient motivation can be absent. Although the most common causes of therapeutic failure are undiscovered secondary causes of hypertension and

lack of patient compliance, in about 10% of cases it can be attributed to resistant hypertension caused by a hyperactivity of the sympathetic nervous system. Increased activation of the sympathetic nervous system is identified as an important factor in the development and progression of hypertension. In this context has been developed catheter-based approach to disrupt the renal sympathetic nerves-renal denervation. Even though this method is promising, criticism is directed at inadequately designed mostly observational studies without 24h ambulatory blood pressure measurement records, coupled with a significant variability in patient response to therapy (14). That is why it is important to finally assess the effectiveness of renal denervation and the influence it might have on reducing cardiovascular morbidity and mortality. Among patients with resistant hypertension it is very important to select patients most likely to have benefit from renal denervation, because they represent a very mixed group of diagnoses.

Resistant hypertension in chronic kidney disease contributes significantly to increased cardiovascular risk and progression of kidney damage. In patients with the salt-sensitive type of hypertension or chronic kidney disease the nigh time drop of blood pressure is not evident, requiring different ingestion time dependent strategies of hypertension medications. Although chronotherapy is not uniformly recommended in the treatment of resistant hypertension, it is a cost-effective strategy for reducing cardiovascular risk. Further investigation is needed to evaluate the importance of chronotherapy on cardiovascular outcomes in resistant hypertension chronic kidney disease patients.

CONFLICT OF INTEREST: NON DECLARED.

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