RESISTANT ARTERIAL HYPERTENSION AND TREATMENT MODALITIES

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Abstract

Hypertension is one of the most common diseases in the general population. Despite the new generation of antihypertensive drugs and improved guidelines, there is still a poor number of patients with well-controlled hypertension. The particular group is patients with resistant hypertension. It is highly prevalent in the general hypertensive population and good control of those patients remains a great challenge. Renal sympathetic hyperactivity is a response mechanism of resistant hypertension. One of the options for those patients is transcatheter renal sympathetic denervation. Recent studies show promising results and it has become a possible therapeutic alternative to treat this group of patients.

Keywords: hypertension, resistant hypertension, renal denervation

Introduction

Hypertension (HT) is a disease with a high prevalence in the general population, with a constant increase in the number of patients. It belongs to the diseases that bring the greatest risk for the occurrence of other cardiovascular diseases. In a large number of cases, the target values are not achieved, despite the use of new generations of antihypertensive drugs and fixed combinations with two or three antihypertensive drugs, which, in addition to the therapeutic effect, contribute to improved adherence. It is known that renal sympathetic hyperactivity is the most important pathophysiological mechanism for the emergence of resistant hypertension (RH). Resistant hypertension includes all groups in which with the help of three or more antihypertensive drugs, one of which is a diuretic, it is not possible to achieve satisfactory blood pressure control and the values are over 160/90 mmHg[1].

Blood pressure target values

Treatment of blood pressure (BP), according to the guidelines of the European Society of Hypertension/European Society of Cardiology, ESH/ESC, 2018 was defined based on a study that included 9,000 patients with high cardiovascular (CV) risk, patients with *diabetes mellitus* or previous stroke were excluded from the study. More intensive BP-lowering treatment (achieved SBP 121 *vs* 136 mmHg) was associated with a 25% reduction in major CV events and a 27% reduction in all-cause death (but no significant reduction in stroke or myocardial infarction). This outcome undoubtedly favors the positive effects of more versus less intensive blood pressure-lowering treatment strategies in high-risk patients. However, this randomized trial does not clarify the optimal blood pressure target value, because the method used for ambulatory blood pressure measurement in Secondary Prevention Reinfarction Israeli Nifedipine Trial, SPRINT (automated unattended measurement) has not been used in any previous randomized trials that provide a database for the treatment of hypertension. The reason that explains such a result is that without supervision, automated blood pressure measurement results in lower values compared to conventional measurement in the doctor's office, due to the absence of the white coat effect. Therefore, it has been suggested that blood pressure values reported in SPRINT may correspond to conventional office blood pressure measurements[2-4].

The recommendation of the hypertension working group of the European Society of Cardiology is that, if drugs are used to treat high blood pressure, the first goal should be to reduce blood pressure to < 140/90 mmHg in all patients. If such therapy is well tolerated, treated blood pressure values should be directed toward a goal of 130/80 mmHg or lower in most patients, although in some groups the evidence is less conclusive. In patients older than 65 years, systolic blood pressure should be between 130 and 140 mmHg and diastolic blood pressure at < 80 mmHg. SBP values should not be lowered to < 120 mmHg. It is important to define the target range because the lower limit can be of great importance if it is below the specified values. In general, when SBP is reduced to < 120 mmHg, in patients enrolled in randomized cohort trials (RCT), ie. in older and more at-risk patients, often with comorbidities and cardiovascular disease, the risk appears to increase and outweigh the benefits[2].

Hypertension therapy

When we talk about the groups of drugs that are used to treat hypertension, the basic five groups are practically the first line of treatment. These include diuretics (thiazide, indapamide), beta blockers, calcium antagonists, (Angiotensin Converting Enzyme inhibitors) ACE inhibitors, and (Angiotensin Receptor Blockers) ARB blockers. For resistant hypertension, along with all the above groups, the drug spironolactone is the most potent and the drug of choice according to current guidelines for the treatment of arterial HT.

Medication adherence is a term that defines whether the patient takes the prescribed therapy or takes it, but not in the prescribed doses and intervals. Adherence is one of the major causes of poor blood pressure control. Poor adherence leads to poor blood pressure control and failure to achieve target values. All of these together increase the number of adverse outcomes, including stroke, myocardial infarction, heart failure, and death. Although the effectiveness of drugs that control blood pressure is clear, there is still a risk of stroke, kidney, and cardiovascular disease. Uncontrolled blood pressure and poor adherence to antihypertensive medications remain major clinical challenges affecting public health. Previous research has identified determinants of poor adherence and explored how to address barriers, improve adherence, and ultimately achieve blood pressure control. Several approaches are successful, although none are superior in improving adherence and better blood pressure control. As the treatment goal of lower systolic blood pressure (< 120 mm Hg), indicated by recent results from systolic blood pressure treatment trials, is integrated into clinical practice guidelines, new standards for blood pressure control are likely to emerge and increasing attention will be paid to dedicate to improving patients' adherence to prescribed therapies to achieve lower target values[5].

Resistant hypertension

Resistant hypertension is usually defined as resistant or refractory when a treatment plan that includes lifestyle considerations and the prescription of at least three different medications (including a diuretic) at optimal doses has failed to reduce both systolic and diastolic blood pressure (DBP) to a threshold. However, according to new data, resistant hypertensives are considered to be those who need four or more drugs for control. Resistant hypertension is highly prevalent among the general hypertensive population and clinical management of this condition remains problematic. Various approaches, including intensified antihypertensive therapy, lifestyle modifications, or both, have largely failed to improve patient outcomes and reduce cardiovascular and renal risk. Since renal sympathetic hyperactivity is the main driver of resistant hypertension, in the last decade renal sympathetic ablation (renal denervation) has been proposed as a possible therapeutic alternative for the treatment of this condition[6].

Numerous sources of evidence, as well as clinical experience, show that resistant hypertension is a frequent category among hypertensive patients and represents a major challenge in treatment. The incidence of resistant hypertension is around 13-14%. The prognosis of patients with resistant hypertension is worse compared to patients in whom good blood pressure control has been achieved, due to damage to the target organs, and more frequent occurrence of cardiovascular and cerebrovascular incidents. Positive effects of pharmacological treatment are expected, as recommended in numerous studies. Appropriate and timely treatment of resistant hypertension is suggested, along with lifestyle changes that contribute to treatment resistance, as well as timely diagnosis and treatment of the causes of secondary hypertension, with the use of medications from several groups. Lifestyle changes, including weight loss, regular exercise, a high-fiber, low-fat, low-salt diet, treatment of obstructive sleep apnea, and moderation of alcohol intake should be encouraged where possible[7].

Medical treatment should be adjusted as much as possible, including the use of a fixed combination of long-acting drugs, to reduce the number of pills prescribed and allow for once-daily dosing. Drugs that can interfere with blood pressure control, mainly (Nonsteroidal Anti-Inflammatory Drugs) NSAIDs, should be avoided in subjects with resistant hypertension, or the least effective dose should be used with rapid titration and withdrawal as soon as possible, with close monitoring of blood pressure when used. Resistance to therapy can often be related to inadequate therapy or lack of diuretic therapy. In most patients, the use of long-acting thiazide diuretics will be most effective, as they usually have inadequate volume expansion. In a blind comparison of hydrochlorothiazide 50 mg and chlorthalidone 25 mg daily, the latter provided a greater 24-hour ambulatory blood pressure reduction. In patients with renal impairment, loop diuretics may be necessary for effective volume and blood pressure control. Due to the high incidence of primary aldosteronism in patients with resistant hypertension, mineralocorticoid receptor antagonists have been found to provide a significant antihypertensive role with previously administered antihypertensive groups in adequate doses and intervals, even with low doses of spironolactone.

Although there is little data regarding the effectiveness of treatment with a fixed combination of three or more drugs, it seems reasonable to combine drugs with different mechanisms of action, such as an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, a calcium channel blocker, and a thiazide diuretic. Fixed combinations with two or three antihypertensives in one pill offer certain advantages over single drugs, including increased efficacy, reduced incidence of side effects, and improved patient adherence.

Nevertheless, resistant hypertension, as a specific subgroup, remains insufficiently studied. Additional data are needed to improve the identification and treatment of these patients. A review of the efficacy of precision multidrug regimens, including new therapies, is needed. In this way, new data on the effectiveness of the new vasodilator, selective endothelin type A antagonist, darusentan, was published. Renal sympathetic hyperactivity is associated with hypertension and its development, development of renal weakness, and heart failure. A recent trial shows that renal denervation leads to a significant and sustained reduction in blood pressure in a group of resistant hypertensive patients, without serious adverse events, as a safe procedure. Renal denervation is an innovative method of treating hypertension, which is based on the reduction or interruption of sympathetic signals to the kidneys, through the denervation of the kidneys using endovascular devices.

In summary, the definition of RH has been modified compared to that of 2008 (American Heart Association, AHA), in four important ways: blood pressure should be measured and the BP threshold for diagnosis and treatment should be under current clinical guidelines practice, patients should take ≥ 3 antihypertensive agents, usually including a long-acting calcium channel blocker (CCB), a renin-angiotensin system blocker (ACE inhibitor or ARB), and a diuretic at maximal or maximally tolerated doses; patients with the white coat effect should not be included in the definition of resistant hypertension; and the diagnosis of resistant hypertension requires the exclusion of non-adherence to antihypertensive drugs[8].

Risks in resistant hypertension

Observational studies using the 2008 criteria have shown that patients with RH are at greater risk for poor outcomes compared to patients without RH. In a retrospective study of > 200,000 patients with hypertension, those with RH had a 47% higher risk of worse outcomes such as myocardial infarction, heart failure, death, stroke, or chronic kidney disease (CKD) over an average of 3.8 years of monitoring. The differences in CV events in this study were largely driven by a higher risk of developing CKD. In another study of > 400,000 patients, compared with patients without resistant hypertension, patients with resistant hypertension had a 32% increased risk of developing end-stage renal disease, a 24% increased risk of an ischemic heart event, a 46% increased risk of heart failure, 14 % increased risk of stroke and 6% increased risk of death. Prospective studies using blood pressure monitoring have reported an almost two-fold increased risk of cardiovascular events in patients with well-defined resistant hypertension compared with those who are well-controlled. Collectively, these studies suggest that resistant hypertension is associated with a significantly higher risk of adverse outcomes and represents an important public health problem.

Resistant hypertension is associated with worse outcomes, especially in patients with comorbidities. In patients with renal impairment, resistant hypertension is associated with a higher risk of myocardial infarction, stroke, peripheral artery disease, heart failure, and all-cause mortality compared with patients without resistant hypertension. Similarly, in patients with ischemic heart disease, RH is associated with higher rates of adverse events, including death, myocardial infarction, and stroke[9-11]. In contrast, RH is not associated with increased adverse clinical events in heart failure patients with reduced left ventricular ejection fraction and may reduce the risk of heart failure-related rehospitalization. Among patients with RH, a group of patients with lower blood pressure is associated with a reduced risk for some cardiovascular events[12].

In the REGARDS study, Reasons for Geographic and Racial Differences in Stroke, uncontrolled RH was associated with a two-fold increased risk of coronary heart disease, compared with controlled RH. Control status was not associated with differences in stroke or mortality. In another study of > 118,000 treated adult patients with hypertension, including > 40,000 individuals with RH, blood pressure control was associated with significantly lower rates of stroke and coronary heart disease, with no difference in incident heart failure rates. Blood pressure control reduced the risk of stroke, coronary heart disease, or heart failure by 13% among those with RH, compared with a 31% lower risk of these outcomes among patients without RH[13]. Although blood pressure control is associated with a lower risk for some CVD outcomes, the benefit of lowering blood pressure may be less in patients with RH compared to patients without RH.

To treat resistant hypertension, it is necessary to rule out secondary hypertension as a cause. Along with numerous etiological factors of secondary hypertension, such as diseases of the adrenal glands, thyroid glands, breathing disorders during sleep, etc, renovascular hypertension is especially important if therapy based on transcatheter renal denervation is planned. This type of therapy specifically requires that renal artery stenosis be excluded as a cause of hypertension.

Renovascular hypertension (RVH) is one of the pathophysiological mechanisms for the occurrence of secondary hypertension, along with numerous other mechanisms. RVH is defined as a condition in which renal artery occlusion or stenosis reduces renal flow to a level that activates the renin-angiotensin-aldosterone system (RAAS) and thereby increases blood pressure. Some of the main causes and mechanisms are fibromuscular dysplasia (FMD) and atherosclerosis, which usually involve different groups of patients. FMD especially affects children and young and middle-aged women[14] and is a systemic arterial disease. Atherosclerotic renovascular hypertension (ATS-RVH) is the most common form in older adults, predominantly men, with multiple risk factors. Its prevalence in the general population of patients

with hypertension ranges between 1 and 8%, depending on the selection of the population, but it can be up to 25-35% in patients with signs of multisite atherosclerosis. RAAS activation occurs when the narrowing of the renal artery lumen in one or both renal arteries reaches a certain threshold, which is usually estimated to be > 75% or may occur even at a lower degree of stenosis if there is post-stenotic dilatation. Increased renin synthesis aims to maintain the glomerular filtration rate (GFR) through marked constriction of post-glomerular arterioles and via raising systemic blood pressure. However, in most patients, at the time of diagnosis, activation of the renin-angiotensin system can no longer be detected for several reasons[15]. It must be considered that renal artery stenosis may be hemodynamically insignificant and may be the result of accelerated atherosclerosis in patients with primary hypertension. Therefore, confirming the diagnosis of renovascular hypertension is a challenging endeavor, as it can only be performed retrospectively if revascularization results in a cure or improvement of HT[16].

Renal denervation (RDN) is an innovative method of treating resistant hypertension, which is effective in reducing or interrupting sympathetic signals to the kidneys and reducing sympathetic activity throughout the body. Numerous studies provide evidence that RDN effectively lowers blood pressure, even in those without concomitant antihypertensive medication. An average reduction in BP of 10 mmHg is estimated to reduce the incidence of cardiovascular events by 25-30%, with no adverse events during a 3-year patient follow-up. The implementation of RDN as an innovative antihypertensive treatment option requires a systematic selection of patients, a multidisciplinary treatment that includes the involvement of endocrinologists and nephrologists in making decisions about this type of therapy, and the opinions and wishes of the patients themselves should also be respected when making decisions[17, 18].

Conclusion

Experiences and scientific evidence regarding the pathophysiology and treatment of arterial hypertension are extensive. With modern antihypertensive drugs and invasive transcatheter therapy (renal denervation), this area is still full of challenges, considering the number of patients that is constantly growing and the number of patients that are poorly controlled. The treatment of patients with resistant hypertension should be focused on optimized and intensified drug therapy with drugs from at least three groups of antihypertensives, with mandatory diuretics. If even with this approach there is no satisfactory blood pressure control, transcatheter renal denervation is a justified therapeutic option. Recent findings during the follow-up of patients treated with transcatheter renal denervation have promising data. Additional research, data, and experiences on a larger number of patients are needed for the wider application of this type of therapy.

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