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Review Article

Treatment of Resistant Hypertension

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Abstract

Resistant hypertension is a blood pressure remaining above goal despite the use of 3 optimally dosed antihypertensive drugs from different classes, with one of the drugs being a diuretic. The 3 drugs should be an angiotensin-converting enzyme inhibitor or angiotensin blocker plus a calcium channel blocker plus a thiazide-type diuretic. Pseudo-resistant hypertension and white coat-resistant hypertension must be excluded. Poor patient compliance, inadequate doses of antihypertensive drugs, inadequate choice of combinations of antihypertensive drugs, poor office blood pressure measurement technique, and having to pay for costs of drugs are factors associated with pseudo-resistant hypertension. Factors contributing to resistant hypertension include obesity, excess dietary sodium, excess alcohol intake, use of cocaine, amphetamines, non-steroidal anti-inflammatory drugs, contraceptive hormones, adrenal steroid hormones, sympathomimetic drugs (nasal decongestants and diet pills), erythropoietin, and licorice, herbal supplements such as ephedra, progressive renal insufficiency, and inadequate diuretic therapy. Secondary causes of resistant hypertension include primary hyperaldosteronism, renal artery stenosis, renal parenchymal disease, and obstructive sleep apnea, coarctation of the aorta, Cushing's syndrome, pheochromocytoma, hyperthyroidism, hypothyroidism, and intracranial tumors. Some data support the use of spironolactone as a fourth drug in the treatment of resistant hypertension if the serum potassium level is ≤ 4.5 mmol/L. New drugs and device therapy are currently under investigation for treatment of resistant hypertension. The Symplicity HTN-3 study showed that renal denervation therapy was not more effective than a sham control arm in treating resistant hypertension.

INTRODUCTION

Hypertension is a major risk factor for cardiovascular events and mortality [1] and occurs in 69% of patients with a first myocardial infarction [2], in 77% of patients with a first stroke [2], in 74% of patients with congestive heart failure [2], and in 60% of patients with peripheral arterial disease [3]. Hypertension is also a major risk factor for dissecting aortic aneurysm, sudden cardiac death, angina pectoris, atrial fibrillation, diabetes, metabolic syndrome, chronic kidney disease, thoracic and abdominal aortic aneurysms, left ventricular hypertrophy, vascular dementia, Alzheimer's disease, and ophthalmologic disorders [1].

The American College of Cardiology Foundation/American Heart Association 2011 expert consensus document on hypertension in the elderly recommended that the blood pressure should be reduced to less than 140/90 mm Hg in patients younger than 80 years at high risk for cardiovascular events [1]. On the basis of data from the Hypertension in the Very Elderly trial [4], these guidelines recommended that the systolic blood pressure (SBP) should be decreased to 140 to 145 mm Hg if tolerated in patients aged 80 years and older [1].

The European Society of Hypertension/European Society of Cardiology 2013 guidelines recommended reducing the SBP s to less than 140 mm Hg in patients at low to moderate cardiovascular risk, diabetics, prior stroke or transient ischemic attack, coronary heart disease, and chronic kidney disease (CKD) [5]. In older patients younger than 80 years with a SBP ≥ 160 mm Hg, the SBP should be lowered to 140-150 mm Hg with consideration of a SBP < 140 mm Hg. In patients older than 80 years with a SBP ≥ 160 mm Hg, the SBP should be lowered to 140-150 mm Hg provided they are in good physical and mental conditions [5].

The 2013 Eighth Joint National Committee (JNC 8) guidelines for management of hypertension recommended reducing the SBP in patients younger than 60 years to less than 140/90 mm Hg and in patients ≥ 60 years to <150 mm Hg if they did not have diabetes or CKD and to < 140 mm Hg if they had diabetes or CKD [6]. The minority view from JNC 8 recommended a SBP goal in patients younger than 80 years with hypertension without diabetes or CKD should be less than 140 mm Hg [7].

A statement from the American Heart Association defined resistant hypertension as a blood pressure remaining above goal

despite the use of 3 optimally dosed antihypertensive drugs from different classes, with one of the drugs being a diuretic [8]. The National Institute for Health and Clinical Excellence guideline suggests that the 3 drugs should be an angiotensin-converting enzyme inhibitor or angiotensin blocker plus a calcium channel blocker plus a thiazide-type diuretic [9].

Pseudohypertension in the elderly is a falsely high SBP resulting from markedly sclerotic arteries which do not collapse under the blood pressure cuff [1]. Pseudohypertension can be confirmed by measuring intra-arterial pressure. White coat hypertension is diagnosed in patients with persistently elevated office blood pressures but normal daytime ambulatory blood pressures. Ambulatory blood pressure monitoring is recommended to confirm white coat hypertension in patients with office hypertension but no target organ damage [1]. Home recordings of blood pressure should also be obtained to avoid excessive blood pressure lowering in patients.

Before a patient is considered to have resistant hypertension, pseudo-resistant hypertension must be excluded [9]. White coat-resistant hypertension which is an elevated office SBP of ≥ 140 mm Hg but a normal home blood pressure or 24-hour ambulatory blood pressure must be excluded [9,10]. Poor patient compliance, inadequate doses of antihypertensive drugs, inadequate choice of combinations of antihypertensive drugs, poor office blood pressure measurement technique, and having to pay for costs of drugs are factors associated with pseudo-resistant hypertension [9,11].

Factors contributing to resistant hypertension include obesity, excess dietary sodium, excess alcohol intake, use of cocaine, amphetamines, non-steroidal anti-inflammatory drugs, contraceptive hormones, adrenal steroid hormones, sympathomimetic drugs (nasal decongestants and diet pills), erythropoietin, and licorice, herbal supplements such as ephedra, progressive renal insufficiency, and inadequate diuretic therapy [9]. Secondary causes of resistant hypertension include primary hyperaldosteronism, renal artery stenosis, renal parenchymal disease, obstructive sleep apnea, coarctation of the aorta, Cushing's syndrome, pheochromocytoma, hyperthyroidism, hypothyroidism, and intracranial tumors [9,12].

Data from the National Health and Nutrition Examination Survey database from 2003 through 2008 estimated the prevalence of resistant hypertension was 8.9% of all United States adults with hypertension [13]. Of 614 patients with hypertension followed in a university cardiology or general medicine clinic, 40 patients (7%) were receiving 4 antihypertensive drugs, and 9 patients (1%) were receiving 5 antihypertensive drugs [11]. In 53,380 patients with hypertension and atherothrombotic disease in the International Reduction of Atherothrombosis for Continued Health (REACH) registry, the prevalence of resistant hypertension was 12.7% with 4.6% receiving 4 drugs and 1.9% receiving 5 or more drugs [14].

However, the best study on the incidence of resistant hypertension found in 205, 750 patients with incident hypertension that 1.9% developed resistant hypertension within a median of 1.5 years from initial therapy [15].

Patients with resistant hypertension have a higher incidence of cardiovascular events [14,15]. Therefore, more effort is needed to improve clinical outcomes in these patients.

Some data support the use of spironolactone as a fourth drug in the treatment of resistant hypertension if the serum potassium level is ≤ 4.5 mmol/L [9,16]. New drugs and device therapy are currently under investigation for treatment of resistant hypertension [17].

At 24-month follow-up after catheter-based renal sympathetic denervation of 153 patients with resistant hypertension, postprocedure office blood pressure was 32/14 mm Hg lower without significant adverse events in the Symplicity HTN-1 study [18]. At 12-month follow-up after catheter-based renal sympathetic denervation of 49 patients with resistant hypertension in the initial renal denervation group, postprocedure office systolic blood pressure was 28.1 mm Hg lower in the Symplicity HTN-2 study [19]. At 6-month follow-up after catheter-based renal sympathetic denervation of 35 patients with resistant hypertension in the crosover renal denervation group, postprocedure office systolic blood pressure was 23.7 mm Hg lower in the Symplicity HTN-2 study [19]. A meta-analysis was performed of 12 studies with a total of 561 patients investigating use of catheter-based renal sympathetic denervation for treating patients with resistant hypertension [20]. These studies included 2 randomized controlled trials with 133 patients, 1 observational study with a control group with 50 patients, and 9 observational studies without a control group with 396 patients. At a median follow-up of 6 months, renal sympathetic denervation caused a lowering of blood pressure of 28.9/11.0 mm Hg [20].

The European Society of Hypertension position paper summarized current evidence, unmet needs, and practical recommendations on use of renal denervation to treat resistant hypertension in hypertension excellence centers [21]. An international expert consensus statement recommended that renal denervation should be considered only in patients whose blood pressure cannot be controlled by lifestyle modification and pharmacologic therapy tailored to current guidelines [22].

Despite these recommendations, this author has stated at medical meetings that renal sympathetic denervation for resistant hypertension needed long-term cardiovascular outcome data not yet available and needed a large-scale prospective, long-term study of patients with resistant hypertension randomized to renal denervation therapy versus a sham procedure control arm.

The recently published Symplicity HTN-3 study was a prospective, single-blind randomized, sham-controlled trial which randomized 535 patients with resistant hypertension in a 2:1 ratio to undergo renal denervation or a sham procedure [23]. The primary efficacy endpoint of change in office SBP at 6 months was a reduction of 14.13 mm Hg for renal denervation versus 11.74 mm Hg for the sham procedure (p not significant) [23]. The secondary efficacy endpoint of change in mean 24-hour ambulatory SBP at 6 months was a reduction of 6.75 mm Hg for renal denervation versus 4.79 mm Hg for the sham procedure (p not significant). There were no significant differences in safety between the 2 groups [23]. Fortunately, renal denervation

therapy had not been approved by the United States Food and Drug Administration for treatment of resistant hypertension. This study is another example demonstrating why appropriate controls are necessary in clinical studies to avoid a placebo effect.

There are some data which suggest that baroreflex activation therapy may be beneficial in patients with resistant hypertension [24-26]. However, an appropriate clinical trial using a randomized sham control arm and long-term cardiovascular outcome data are needed to assess the efficacy and safety of this procedure.

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