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Assessing and managing resistant hypertension

Possible causes of refractory high blood pressure include inappropriate drug doses and combinations, poor adherence to therapy, secondary causes, and patients truly resistant to current therapy.

ABSTRACT: Resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes, including one diuretic, prescribed at optimal dose. Estimates suggest 20% to 30% of patients with high blood pressure have resistant hypertension. A practical approach to assessing resistant hypertension involves determining whether BP was measured correctly, evaluating whether appropriate drug doses and combinations are being used, evaluating patient adherence to therapy, considering patient characteristics, and determining if other medications (including over-the-counter drugs and herbal preparations) are being used. Managing refractory hypertension involves addressing the issues identified in the initial assessment, intensifying dietary sodium restriction and diuretic therapy, considering sympathetic nervous system activation and the need to add appropriate drugs, using mineralocorticoid antagonists, investigating for secondary causes of hypertension, and considering the use of newer/investigational drugs and devices if necessary.

Resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes, including one diuretic, prescribed at optimal doses.[1] Some investigators estimate that 20% to 30% of patients with high blood pressure appear to have resistant hypertension. A practical approach to assessing and managing resistant hypertension includes reviewing patient factors and taking into account some newer concepts in the pathogenesis and management of resistant hypertension (see **Table 1**).

Assessment

The first step in the diagnosis of resistant hypertension requires the physician to review whether blood pressure has been measured correctly (see "Measurement of blood pressure" in this issue) and ensure that office-induced blood pressure elevation (white-coat hypertension) has not influenced the diagnosis. After a diagnosis of resistant hypertension has been confirmed, the physician must consider the many possible causes (see **Table 2**).

Drug doses and combinations

While some investigators contend that the physician's choice of inadequate doses, inappropriate combinations of antihypertensive agents, and poor patient adherence do not contribute to resistant hypertension, other investigators consider these to be factors. The choice of antihypertensive agents should be reviewed to ensure that the patient is receiving an optimal combination of drugs at appropriate doses, and that a diuretic is included in the combination therapy. For example, it is preferable that combination therapy for patients taking an ACE inhibitor include a dihydropyridine calcium channel blocker (CCB) such as amlodipine.[2] This recommendation is based on the ACCOMPLISH trial, which compared an ACEI plus dihydropyridine CCB therapy with an ACEI plus hydrochlorothiazide therapy. The former therapy was significantly better than the latter, with the trial primary endpoint being the composite of myocardial infarction, stroke, cardiovascular death, hospitalization for angina, resuscitated cardiac arrest, and coronary revascularization.[3] Use of inadequate drug doses despite persistent blood pressure elevation may be part of the phenomena labeled clinical inertia, which occurs when health care

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providers do not initiate or intensify therapy appropriately when following patients with chronic problems such as hypertension.[4] Concerns about the potential adverse effects of some antihypertensive agents may explain why some health care providers appear willing to accept small blood pressure elevations in their patients rather than treating them vigorously to attain accepted target levels.[5]

Patient factors

Patient adherence to recommended therapy should be examined, especially since compliance with drug regimens for asymptomatic conditions such as hypertension is notoriously poor. Patients may become confused over which drugs to take or may find frequent dosing schedules incompatible with their routines. Asking specific questions, obtaining collateral information from a partner or family member, and pill counting are all relatively simple ways to uncover this problem. Collaborative health care models with a physician, home care nurse, and pharmacist can be effective in identifying and managing this problem. Even after adherence improves, however, a large number of patients will still be found to have resistant hypertension.[6]

Patient characteristics should also be considered when assessing resistant hypertension. Lower rates of blood pressure control have been identified in both overweight and obese patients,[7] and achieving blood-pressure control is known to be more difficult in the obese than in the lean hypertensive patient. Potential mechanisms for obesity-related hypertension include activation of the sympathetic nervous system or the renin-angiotensin-aldosterone system, impaired urinary sodium excretion, development of chronic renal disease, increased amounts of leptin, and endothelial dysfunction.[8]

Table 1. An approach to assessing and managing resistant hypertension.

- Assess whether BP was measured correctly.
- Evaluate whether appropriate drug doses and drug combinations are being used.
- Evaluate patient adherence to medications.
- Consider patient characteristics.
- Review other medications being used by patient, including over-the-counter drugs and supplements.
- Consider sodium excess and intensify dietary sodium restriction and diuretic therapy.
- Consider sympathetic nervous system activation and add appropriate drugs.
- Consider using mineralocorticoid antagonists.
- Investigate for secondary causes of hypertension.
- Consider using newer/investigational drugs, devices, or procedures.

Table 2. Potential causes of resistant hypertension.

- Inappropriate drug doses and combinations
- Poor patient adherence to therapy
- Patient conditions and habits
  - Obesity
  - Sleep apnea
  - Excessive alcohol consumption
- Other medications and supplements
  - Nonsteroidal anti-inflammatory drugs
  - Oral contraceptives
  - Corticosteroids and anabolic steroids
  - Sympathomimetics
  - Cocaine, amphetamines
  - Calcineurin inhibitors (cyclosporin, tacrolimus)
  - Erythropoitein and its analog
  - Antidepressants (monoamine oxidase inhibitors, certain serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors)
  - VEGF inhibitors
  - Over-the-counter drugs (decongestants, cold-flu remedies)
  - Herbal preparations (ephedra, ma huang, bitter orange, licorice)
- Secondary causes
  - Renovascular disease/renal artery stenosis
  - Chronic kidney disease
  - Certain neurological disorders
  - Endocrine system disorders
    - primary hyperaldosteronism
    - hyperthyroidism
    - pheochromocytoma
    - acromegaly
    - hyperparathyroidism
    - carcinoid tumor
    - congenital adrenal hyperplasia
- Volume overload
  - Excessive salt intake
  - Increased sodium retention
- Sympathetic nervous system activation
- Renin-angiotensin-aldosterone system activation

Obstructive sleep apnea is prevalent in patients with resistant hypertension. The intermittent hypoxemia and increased upper airway resistance it causes can increase sympathetic nervous system activity, which can in turn increase blood pressure and promote fluid retention.

Consumption of large amounts of alcohol is another cause of blood pressure elevation. The mechanisms involved in alcohol-generating hypertension appear to include the effects of vasoconstriction, modification of smooth muscles, and calcium transport.[8] In addition, heavy drinkers may be less adherent to antihypertensive therapy.

Other medications and supplements

A review of a patient's medications and supplements can identify agents that might increase blood pressure or modulate the action of antihypertensive drugs, blunting their efficiency. A number of agents with the potential to increase blood pressure are listed in **Table 2**. Some of the data linking these agents to resistant hypertension, are, however, controversial. For example, in the case of nonsteroidal anti-inflammatory drugs (NSAIDs), the magnitude of effect varies among studies and depends in part on the type of NSAID. Replacing NSAIDS with acetaminophen is helpful, although it may not totally solve the problem, as recent data suggest that acetaminophen can also produce a small increase in blood pressure.[9]

Secondary hypertension

Secondary causes of hypertension are well described in the literature and some are listed in **Table 2**. After history taking, a physical examination, and routine laboratory tests are completed, clinical judgment will determine the exact place in the assessment and management of resistant hypertension to begin considering secondary causes. Because essential hypertension is far more common than secondary hypertension, current guidelines recommend investigating for secondary causes only when hypertension is resistant to medications or the history, physical examination, or routine testing suggest a secondary cause. A specific set of investigations is required for each condition in the long list of well-known causes of secondary hypertension. Endocrine and renal causes are the most common. Aldosterone excess leading to hypertension, metabolic alkalosis, hypernatremia, and hypokalemia can result from an aldosterone-producing adenoma, bilateral adrenal hyperplasia, glucocorticoid-remediable aldosteronism, or rare familial syndromes. In fact, resistant hypertension is the condition most likely to prompt investigation for primary hyperaldosterone states.[10] Renovascular disease, another common cause of secondary hypertension, is more frequent in older individuals, patients with diabetes mellitus, cigarette smokers, and patients with atherosclerotic lesions at other vascular beds. When a patient has clinical evidence of Cushing syndrome, coarctation of the aorta, a family history of polycystic kidney disease, or hypokalemia in the absence of diuretic treatment, the clinician should pursue appropriate investigations before considering the other potential causes of hypertension described below.

Sodium excess and volume overload

Sodium and fluid retention play an important role in resistant hypertension. A randomized crossover evaluation of low-sodium (50 mmol/24 hours $\times$ 7 days) and high-sodium diets (250 mmol/24 hours $\times$ 7 days) separated by a 2-week washout period showed that when compared with a high-sodium diet, a low-sodium diet reduced systolic blood pressure by 22.7 mm Hg and diastolic blood pressure by 9.1 mm Hg.[11]

Pressure-natriuresis is the increase in sodium excretion that occurs with elevated blood pressure. Normal function of the pressure-natriuresis mechanism minimizes further blood pressure increases and possibly prevents hypertension, since any elevation of blood pressure increases the sodium and water excretion that would reduce the blood volume and blood pressure. In patients with hypertension, abnormal pressure-natriuresis leads to higher levels of blood pressure, which indicate a lesser amount of sodium excretion for a similar increase in blood pressure. Relatively more salt retention occurs in a hypertensive patient than a normotensive patient when blood pressure rises to the same level. Patients with resistant hypertension may require more sodium restriction to lower their blood pressure.

Other mechanisms, conditions, and drugs implicated in the pathogenesis of resistant hypertension include renal artery stenosis, increased renin-angiotensin-aldosterone system activity, increased renal sympathetic nervous system activity, nitric oxide deficiency, oxidative stress, hyperaldosteronism, obstructive sleep apnea, and vasodilator medications.

Sympathetic activation

Chronic activation of the sympathetic nervous system has been implicated in the production of hypertension for many years. Before the advent of antihypertensive drugs, surgical denervation was an established treatment strategy. There has been a resurgence of interest in sympathetic denervation based on studies using sympathetic nerve recording and norepinephrine spillover methodology, which show

there is a twofold or threefold increase in sympathetic nervous outflows to the kidneys, heart, and skeletal muscle vasculature in patients with essential hypertension.[12] Activation of the sympathetic nervous system has also been implicated in hypertension associated with obstructive sleep apnea and obesity. Some investigators contend that sympathetic nervous system activation plays a dominant role in 50% of essential hypertension cases. Beta-blockers, alpha-blockers, and centrally acting antihypertensive drugs (clonidine, alpha methyldopa) provide a potential benefit for patients when added to previous therapy for resistant hypertension.

Newer concepts in the pathogenesis and management of resistant hypertension

While newer antihypertensive agents have received more attention than sodium restriction in the past, the role of sodium in resistant hypertension has achieved much more attention recently. Sodium retention can be an important player in any type of resistant hypertension, and may play an even greater role in older individuals, patients with obstructive sleep apnea, and patients with renal disease. Dietary restriction of sodium is a fundamental aspect of managing resistant hypertension, and fortunately there are many resources for patients who need to reduce sodium intake (see "Diagnosis of hypertension and lifestyle modifications for its management" in this issue). As well, drug regimens need to ensure that patients are on appropriate doses of diuretics.

Recent studies have reinvigorated an old field by identifying the roles of aldosterone excess and the mineralocorticoid receptor (MR) in hypertension. In a study published in 2003, treatment with the MR antagonist spironolactone was found to substantially reduce blood pressure in a spectrum of patients with resistant hypertension, regardless of whether primary hyperaldosteronism was present.[13] In another study, spironolactone produced a significant decrease in systolic blood pressure and left ventricular mass in patients both with and without high aldosterone levels.[14] Aldosterone antagonism benefits patients with and without aldosterone excess because mineralocorticoid receptors play a role in hypertension regardless of whether there is a systemic increase in aldosterone.[15] CNS administration of aldosterone increases BP, an effect MR antagonists address by blocking the CNS mechanisms that produce hypertension. Interestingly, in a study of obstructive sleep apnea, spironolactone not only significantly lowered blood pressure but also reduced the severity of the sleep apnea itself.[16]

Sodium retention can be an important player in any type of resistant hypertension, and may play an even greater role in older individuals, patients with obstructive sleep apnea, and patients with renal disease.

Device- and procedure-based therapy

Recognition of drug-resistant hypertension has renewed enthusiasm for approaches based on devices and procedures. One promising therapy involves implanting a pulse generator (carotid baroreceptor activation), and another relies on applying radiofrequency energy (renal sympathetic denervation).

Reduction in blood pressure from carotid baroreceptor activation is a fundamental physiological response that was used to reset baroreflexes and control hypertension mainly in the late 1950s and 1960s. The introduction of antihypertensive drugs stopped further development of this approach until recently. A new device uses an implantable pulse generator, carotid sinus leads, and a programmer system that communicates with the implantable pulse generator and allows for noninvasive programming and adjustments in the stimulation parameters.[17] Recent clinical trial results are encouraging. Patients with resistant hypertension on a median of five antihypertensive drugs experienced a 21/12 mm Hg reduction in BP from a baseline of 179/105 mm Hg.[18] As with all devices, though, long-term studies are needed to evaluate efficacy and safety.

Another therapy focuses on the renal sympathetic nerves, which are almost exclusively noradrenergic (i.e., they release few other neurotransmitters) and innervate the renal vasculature.[19] Stimulation of these nerves leads to an increased renin secretion rate, increased tubular sodium reabsorption, and decreased renal blood flow.[19]

Sympathetic nervous system hyperactivity has been observed across a spectrum of patients with hypertension and especially in patients with chronic kidney disease. The renal denervation procedure involves femoral artery catheterization. The tip of the catheter is placed in the renal artery and radiofrequency energy is then applied to the vascular wall to provide heat to the sympathetic nerves located in the adventitia.[19] In a clinical trial that randomly allocated patients to renal denervation or control groups, blood pressure levels were significantly reduced by 32/12 mm Hg in the renal denervation group and did not differ from baseline in the control group (change of 1/0 mm Hg).[20] Several Canadian centres have started using this technique for patients with hypertension that persists after all other strategies have failed.

Summary

Patients who do not attain goal or target blood pressure levels need to be assessed. A systematic approach to evaluating these patients and their nonpharmacological and pharmacological treatment programs should be able to improve blood pressure control. Some newer approaches may need to be considered for patients whose blood pressure control is not optimal in order to prevent the development of the severe complications of hypertension, which include heart failure, myocardial infarction, stroke, and end-stage renal disease.

Competing interests

None declared.

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