

Resistant hypertension

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Resistant hypertension is most often due to insufficient medical therapy. With a patient history, physical examination and focused laboratory tests, sufficient information can be gathered to lead to further directed medical therapy, which most often includes a diuretic as part of the drug regimen. Patients may require four or more classes of antihypertensives, some at high doses to achieve control. The clinician must be prepared to use sufficient medications at sufficient doses to achieve blood pressure targets. Referral to a hypertension specialist is appropriate if blood pressure remains uncontrolled despite therapy with three antihypertensive medications.

Key Words: Hypertension; Resistant hypertension

Resistant hypertension is defined by a lack of response to therapy with three or more medications and is evidence of a more severe stage of hypertension, with over a fourfold greater risk of cardiovascular events compared with hypertensive patients achieving blood pressure targets (1). The Joint National Committee's recommendations on high blood pressure (2) define resistant hypertension as "the failure to reach goal blood pressure despite full doses of an appropriate 3 drug regimen including diuretics". The European Society of Hypertension definition (3) is "hypertension resistant or refractory to lifestyle measures and at least three medications, including a diuretic to lower blood pressure to target". These definitions are reasonable and would then be modified by the urgency to treat based on the actual stage of blood pressure, with higher stages indicating greater urgency to achieve control. The Canadian Hypertension Education Program (CHEP) has not developed a recommendation specific to resistant hypertension because of the lack of randomized controlled trials specific to treating the condition.

ETIOLOGY AND PATHOPHYSIOLOGY

The main categories to consider for patients with resistant hypertension are presented in Table 1. Longstanding uncontrolled hypertension leading to resistant hypertension is most often the result of a drug regimen lacking a diuretic, or insufficient antihypertensive classes and dosages (4). Epstein (5) has described the common clinical characteristics of patients with resistant hypertension. These include obesity, diabetes, chronic kidney disease, black race, female sex and left ventricular hypertrophy. To these, Pickering (6) has added older age, and reviewed the literature associating each characteristic with arterial stiffness – a major component of arterial blood pressure. High blood pressure itself causes arterial stiffness and, if uncontrolled over time, it likely also leads to resistance to therapy. Conversely, there are anecdotal reports that over time (months to years), after blood pressure is brought to target, the dosage and number of antihypertensive agents can be reduced. Resistant hypertension may also be secondary to other medical conditions, most often chronic kidney disease or primary hyperaldosteronism as well as renovascular disease and obstructive sleep apnea (7). Low potassium and target organ damage, including

Hypertension rebelle

L'hypertension rebelle est le plus souvent attribuable à un traitement médicamenteux insuffisant. À partir de l'anamnèse, de l'examen physique et d'analyses de laboratoire ciblées, on peut obtenir assez d'informations pour orienter le traitement médicamenteux, qui inclut souvent, entre autre, un diurétique. Pour obtenir une bonne maîtrise de leur TA, les patients peuvent avoir besoin de quatre classes différentes d'antihypertenseurs ou plus, parfois à doses élevées. Le médecin doit être préparé à utiliser suffisamment de médicaments aux doses adéquates pour obtenir les chiffres tensionnels visés. On adressera le patient à un spécialiste de l'hypertension si sa TA demeure incontrôlée malgré un traitement comprenant trois antihypertenseurs.

TABLE 1
The main categories to consider for patients with resistant hypertension

Categories of resistant hypertension
Longstanding uncontrolled hypertension
Secondary hypertension
Nonadherence to therapy
Interfering medications
Lifestyle factors
Epidemiology

albuminuria, retinopathy and left ventricular hypertrophy, were more frequent in those found to have true resistant hypertension compared with those with white coat hypertension (8).

Nonadherence to therapy may be a much more common cause of resistant hypertension than appreciated, as reviewed by Park and Campese (9), who make the distinction between apparent resistance from lack of patient adherence as well as ineffective physician prescribing, versus true resistance. Clues to patient nonadherence are gathered by a careful patient history including a review of prescription refills. Other patient behaviours may lead to resistant hypertension. This includes taking agents that interfere with antihypertensive therapy such as nonsteroidal anti-inflammatory agents, which interfere with antihypertensives by blocking prostaglandins and inducing sodium retention. Agents that stimulate the sympathetic nervous system, often found in cold remedies, also interfere with blood pressure control. Other lifestyle factors, particularly indiscriminate sodium intake, have an impact on drug efficacy, particularly for diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Excessive alcohol intake, obesity and a sedentary lifestyle also contribute to the need for more antihypertensive therapy.

The true incidence of resistant hypertension is not known. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study (10), 27% of subjects required three or more medications. Epstein (5) estimates that approximately 15% of

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TABLE 2
Stepwise approach to addressing the causes of resistant hypertension

Steps to approach the causes of resistant hypertension
Have the blood pressure measurements been correct and has the 'white coat' effect been ruled out?
Is the patient compliant with pharmacotherapy and other advice?
Are the drugs appropriate for the patient (eg, beta-blockers and angiotensin-converting enzyme inhibitors may not be as efficacious in patients of African origin)?
Are there interfering substances (eg, nonsteroidal anti-inflammatory drugs, high salt intake)?
Is there a secondary cause?
Are the drugs too short acting (eg, some drugs, such as captopril, have a short half-life and need to be dosed multiple times per day)?
Are the combinations appropriate (eg, angiotensin-converting enzyme inhibitors and beta-blockers may not give an additive antihypertensive effect) and is a diuretic part of a three-drug regimen?
Is the dosage of all drugs sufficient and are clinically proven antihypertensive doses being used?
Is there renal insufficiency and should the patient be on a loop diuretic?
Are there pathophysiological considerations that are preventing or delaying achievement of blood pressure targets (eg, obesity, advanced atherosclerosis)?

the ALLHAT population had resistant hypertension, pointing out that this is a similar number to those with uncontrolled hypertension despite three medications in the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) (11) and Valsartan Antihypertensive Long-term Use Evaluation (VALUE) (12) studies. Renovascular disease is prevalent in approximately 20% of those with hypertension resistant to combinations of two antihypertensive medications (13). In addition to renal causes, adrenal hypertension is being recognized with increasing frequency – 20% in one small series of resistant hypertensive patients (14). Aldosterone not only stimulates sodium retention, but as recently reviewed by Duprez (15), it also leads to increased arterial stiffness, endothelial dysfunction and central effects with impaired baroreflex function.

DIAGNOSIS AND DIAGNOSTIC TESTS

Before diagnosing resistant hypertension, care should be taken to ensure that blood pressure measurements are accurate and reflective of the true blood pressure. Improper blood pressure measurement (eg, using too small a cuff, or white coat hypertension) can lead to a misdiagnosis of resistant hypertension. Indeed, in some series, over 50% of apparent resistant hypertension was actually due to improper or inaccurate blood pressure measurement (16). Thus, according to CHEP recommendations (16), great care should be taken in the measurement of blood pressure and alternate means of blood pressure measurement, such as home or ambulatory blood pressure monitoring, should be utilized when appropriate. In fact, apparent resistant hypertension is an indication for ambulatory blood pressure monitoring, according to the CHEP recommendations (16). White (17) has further reviewed the role of ambulatory blood pressure monitoring, which can identify those whose office blood pressure does not reflect their true blood pressure, either due to masked hypertension or a white coat effect (17).

When faced with patients whose blood pressure is truly uncontrolled despite three antihypertensive medications, it is appropriate to refer to a specialist in hypertension. As part of the evaluation of these patients, a thorough history to determine whether lifestyle factors or drug adherence are playing a role is indicated. Laboratory evaluation should include potassium, urea and creatinine levels to assess renal function, and a urine dipstick for albumin and hemoglobin. An ultrasound for renal size will help to identify those with small kidneys

typical of nondiabetic medical renal disease, or asymmetrical kidneys often seen in renovascular disease. Further evaluation will be determined by the outcomes of these tests, and the history and examination. A suggested stepwise approach for the management of resistant hypertension is presented in Table 2.

All of the issues noted in Table 2 are discussed in appropriate sections of the 2008 CHEP recommendations, but are collated here to provide a systematic approach to managing resistant hypertension. Although the temptation is frequently to search for secondary causes as the basis of resistant hypertension, in reality, the causes of resistant hypertension are much more mundane. Depending on the series, most apparently resistant hypertension is due to causes such as medication noncompliance, and inadequate drug doses or combinations (4,18). Thus, merely by following the CHEP guidelines for both diagnosis and treatment, resistant hypertension should become far less common, or its causes much more easily identified and treated.

MANAGEMENT

Most resistant hypertension can be controlled with the addition of more medications and higher medication doses in addition to lifestyle management. Lifestyle changes should include a reduction of sodium intake to below 100 mmol/day, alcohol intake of fewer than 14 drinks per week for men and 10 per week for women, as well as regular exercise. For those with obstructive sleep apnea, in addition to these lifestyle measures, continuous positive airway pressure may also be of benefit (19). Following the CHEP recommendations for adding drugs together into appropriate combinations, for patients resistant to two or three medications, a diuretic should be part of the regimen because the absence of a diuretic may be the cause of nonresponsiveness. Typically, combining agents from the list of those recommended for the initial therapy of hypertension leads to control. Initial combinations of thiazide diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with a calcium channel blocker often leads to control, particularly because the almost linear dose response to calcium channel blockers allows an up-titration of these agents. Hypertension specialists will often exceed the dose of calcium channel blocker recommended in the product monograph, with appropriate counselling of their patients. The addition of other agents is often tailored according to specific patient determinants. Long-acting alpha-blockers such as doxazosin are particularly appealing in older men who may have prostate disease, unless they are already on prostate therapy with an alpha-blocker. Spironolactone or eplerenone, a specific aldosterone antagonist, may be very effective, particularly in those with low or low-normal potassium levels (20). Other commonly used agents include hydralazine in multiple daily divided doses, usually with a beta-blocker for heart rate control, methyldopa and clonidine. The use of these agents must be tempered by their side effect profile; in particular, clonidine should be used with caution, if at all, in patients in whom drug adherence is in question, because suddenly discontinuing it may lead to sympathetic rebound. Minoxidil leads to severe salt and water retention, and its role outside of patients on dialysis is limited. A new class of agents – the direct renin inhibitors – has now become available, with aliskiren the first of its class. Early evidence indicates an additive effect when combined with other agents. The role that this class of agent will play in hypertension will evolve with the evidence. Chronic disease models of care involving pharmacists (21) and by extension, other members of the multidisciplinary team, are helpful to manage this chronic disease. We are also reminded by Redon (22) that focusing on the numbers alone in these high-risk individuals is not sufficient and attention must be paid to global cardiovascular risk.

SUMMARY

Resistant hypertension is most often due to a failure to treat hypertension appropriately. Referral to a hypertension specialist is appropriate. Patient history, physical examination and focused laboratory tests are usually sufficient to gather information to lead to further directed medical therapy, which most often includes a diuretic as part of the drug regimen. Patients

may require four or more classes of antihypertensive drugs, some at high doses, to achieve control. Following longstanding achievement of blood pressure control, it may be possible to reduce the number of drugs and their dosages, and still achieve blood pressure targets.

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