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Treatment Resistant Hypertension

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Abstract

Treatment resistant hypertension is defined as a blood pressure not achieving goal blood pressure (<140/90 mmHg) with a combination of three or more antihypertensive drugs. There are several causes for patients not responding to antihypertensive medication. One of the major reasons is non-compliance to the treatment often due to real or perceived side effects or due to a great number of medications and frequent dosing. Exogenous substances, most frequently, non-steroidal anti-inflammatory drugs, and, often not recognized, over-the-counter medications containing ephedrine or pseudo-ephedrine, can reduce the effect of antihypertensive drugs. Obesity and obstructive sleep apnea oppose antihypertensive drug effects by several mechanisms but predominantly by an increase in the activity of the sympathetic and renin-angiotensin-aldosterone systems. White coat hypertension as a cause of treatment resistance is suspected if there is no target organ damage or if the patients complain of symptoms of hypotension during antihypertensive treatment. Secondary forms of hypertension, although comprising only about 5% of patients with treatment resistant hypertension, are important to identify as they may represent a curable form of hypertension.

Key words: antihypertensive treatment, treatment resistance, refractory hypertension, secondary hypertension.

Treatment is directed at identifying and if possible, remove or treat the cause of treatment resistance. Multidisciplinary patient education, involving family members and/or pharmacist, is important to increase compliance and to deal with side effects. Patients' history usually reveals the presence of exogenous substances. White coat hypertension can be assessed by ambulatory blood pressure monitoring or home blood pressure measurement. Weight loss in obese patients and continuous positive airway pressure in patients with obstructive sleep apnea render them susceptible to antihypertensive treatment and lower blood pressure significantly. Secondary forms of hypertension are treated by removal or treatment of the underlying cause. A rational drug combination is important and should include a diuretic. Often, additional antihypertensive drugs have to be added to achieve blood pressure control.

Treatment-resistant or refractory hypertension is defined as a blood pressure not achieving a target systolic blood pressure below 140 mmHg or a diastolic blood pressure below 90 mmHg on a combination of three or more antihypertensive drugs. The purpose of defining treatment-resistant hypertension is to alert caregivers to search for and eliminate or treat possible causes that prevent an appropriate response to antihypertensive treatment. There are several causes for resistance to treatment and therefore the exact prevalence of treatment-

resistance is not known and may also vary greatly according to the type of the patient population studied, whether the prevalence was studied in the hypertensive population in a cross-sectional approach or in more specialized clinics. Results from antihypertensive treatment trials are more reliable since the aim of these studies often was to achieve a target blood pressure, usually a blood pressure below 140/90 mmHg. In one of the largest antihypertensive treatment studies, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the goal systolic blood pressure of less than 140 mmHg was not achieved in 33% and the goal diastolic pressure of less than 90 mmHg was not achieved in 8% receiving a combination of three or more antihypertensive drugs[1]. In the older hypertensive population attainment of systolic blood pressure goal represents a major problem[2]. Several causes, sometimes combined, can lead to resistance to antihypertensive treatment[3].

Lack of adherence to antihypertensive treatment.

Although this does not represent true resistance to treatment, it represents a major reason for lack of blood pressure control[4]. A Canadian study[5] revealed that 50% of patients do not refill their prescriptions after 41/2 years of treatment. Since it is difficult to assess a patient's adherence to treatment, the magnitude of this problem might, if anything, be even greater. There are many reasons for non-adherence including real or perceived side effects, multiple drugs and frequent dosing, as well as forgetfulness, particularly in the elderly, societal, cultural and financial aspects as well as lack of physician motivation to pursue attainment of goal blood pressure and to follow treatment recommendations[6].

Side effects (adverse reactions)

Side effects can be real or perceived and account for a major reason for failure to reach target blood pressure. To distinguish between real or perceived side effects can be difficult but certain characteristics can be helpful. Real side effects are usually typical for a particular drug or class of drugs while the symptoms related to perceived side effects often are the same or are similar for each drug and mostly are of a non-specific nature or are vague e.g. tiredness, "pain allover", "just not feeling well", nausea, "funny head", etc. An important reason for perceived side effects is anxiety[7] and the fear of ingesting a "chemical substance" which is enforced by the obligatory published number of side effects in the packet insert.

Exogenous substances, factors

A great number of exogenous substances or factors can lead to treatment resistance by opposing the antihypertensive drug effect. Table 1 summarizes the most frequent exogenous causes. Among the most frequent culprits are non-steroidal anti-inflammatory drugs[8]. Non-steroidal anti-inflammatory drugs oppose the action of antihypertensive drugs by raising the blood pressure through sodium and volume retention secondary to blockade of the renal vasodilatory prostaglandins[9]. Excessive alcohol intake raises blood pressure and leads to treatment resistance; the mechanism that lead to hypertension and treatment refractoriness are not well known[10]. Through its potent vasoconstrictor effect, cocaine can lead to severe hypertension often also causing stroke and myocardial infarction. Often overlooked, because of their over-the-counter availability, are nasal decongestants containing ephedrine or pseudo-ephedrine.

Table 1. Exogenous substances and factors that can lead to resistance to antihypertensive blood pressure lowering

Non-steroidal anti-inflammatory drugs
Cyclooxygenase-2 inhibitors
Corticosteroids, anabolic steroids
Oral contraceptives, sex hormones
Ephedrine, pseudoephedrine (nasal decongestants)
Alcohol
Stimulants (cocaine, amphetamine)
Erythropoietin and analogues
Calcineurin inhibitors (cyclosporin, tacrolimus)

Obesity

Obesity represents a major reason for lack of response to antihypertensive treatment and control of blood pressure[1,11,12]. That obesity can be the cause of resistance to antihypertensive treatment is supported by the observation that losing weight often lowers blood pressure and restores responsiveness to treatment. The mechanisms whereby obesity increases blood pressure are not well defined but are considered to include salt and water retention as well as stimulation of the sympathetic and renin-angiotensin-aldosterone systems.

White coat hypertension

The prevalence of white coat hypertension varies between studies and according to the blood pressure cut-off levels for the definition of white coat hypertension but may be as high as 20%[13]. Therefore, white coat hypertension has to be considered as a possible cause for treatment resistant hypertension. Symptoms of over-treatment (mainly postural hypotension) with increasing antihypertensive treatment as well as the absence of target organ damage may draw attention to the presence of white coat hypertension. The diagnosis is made by ambulatory or home blood pressure measurements and antihypertensive treatment will have to be guided by these out-of-office blood pressure measurements.

Pseudohypertension

The classical form of pseudohypertension is caused by extreme stiffness of the brachial artery and is diagnosed by using the Osler maneuver which implies that the radial artery is still palpable even if the blood pressure cuff is inflated above the systolic blood pressure[14]. Due to the stiffness of the larger arteries, these patients, mostly elderly, respond poorly to antihypertensive treatment A less classical but more frequent reason for pseudohypertension is the use of too small a cuff size particularly in obese patients[15].

Secondary forms of hypertension

Although secondary forms of hypertension comprise about 5% or less of all hypertensives, it is important to recognize and diagnose them because they may represent a curable form of hypertension. The most frequent forms of secondary hypertension are listed in table 2. Renal artery stenosis occurs more frequently in the elderly hypertensive patients due to the greater prevalence of atherosclerotic disease and respective lesions in the renal arteries are usually located at the ostium of the renal artery. Atherosclerotic lesions comprise about 90% with the remaining 10% presenting as fibromuscular dysplasia. Renal artery stenosis has to be suspected in patients with recurrent flash pulmonary edema due to sudden cardiac diastolic dysfunction. A reduced renal function with an increase in serum creatinine by more than 30% particularly following treatment with an ACE inhibitor or an angiotensin receptor blocker, points to the presence of bilateral renal artery stenosis. Often, serum potassium is low because of secondary hyperaldosteronism.

Table 2. Secondary forms of hypertension and some of their characteristcs

Renal parenchymal diseases Creatinine clearance, proteinuria, specific renal pathology, edema
Renovascular disease (renal artery stenosis) Recurrent pulmonary edema, abdominal bruit, hypokalemia, renal failure
Primary hyperaldosteronism Hypokalemia: spontaneous <3.5 mmol/L, on diuretic <3.0 mmol/L
Pheochromocytoma Paroxysmal headaches, palpitations, anxiety, diaphoresis
Cushings syndrome/disease Clinical presentation, elevated free cortisol, hypokalemia
Hyperparathyroidism Elevated serum calcium, parathyroid hormone, gastric/duodenal ulcer
Carcinoid syndrome Diarrhea, flushing, increased 5-hydroxyindolacetic acid excretion
Obstructive sleep apnea Typical sleep pattern, daytime sleepiness, often associated obesity
Coarctation of the aorta Blood pressure difference upper/lower extremities, typical bruit
Tumor of the central nervous system Specific neurological signs, hyponatremia

In patients with chronic kidney disease resistance to antihypertensive treatment is usually due to the absence of a diuretic in the antihypertensive drug combination or insufficient diuretic treatment since treatment resistance is mostly due to sodium and volume retention.

The prevalence of primary hyperaldosteronism has been reported as high as 20% in patients with treatment-resistant hypertension[16,17]. The clinical hallmark is a low serum potassium, below 3.5 mmol/L in patients who are not on a diuretic and below 3.0 mmol/L for those on a diuretic often with the associated symptoms, e.g. muscle weakness, cramps particularly during exercise due to the catecholamine-induced and beta-receptor-mediated intra-cellular movement of potassium.

A pheochromocytoma has to be suspected when the three cardinal symptoms, palpitations, headache, sudden episodes of anxiety are present with an attendant sudden rise in blood pressure and tachycardia[18].

Sleep apnea (apnea/hypopnea index of 10 events per hour or greater) probably represents the most frequent secondary cause of treatment-resistant hypertension[19,20,21]. The cause of the resistance to antihypertensive treatment in patients is not well known but includes an increase in sympathetic nervous system[22] and renin-angiotensin-aldosterone activity most likely due to frequent episodes of hypoxemia [23]. Increased urinary aldosterone excretion was found in patients with sleep apnea[24]. Because of the frequent combination of obesity and sleep apnea[25], both conditions may be responsible for the antihypertensive drug resistance and thus, it may be difficult to separate their respective contribution to the treatment resistance particularly as both conditions seem to use similar pathways to cause treatment resistance.

Coarctation of the aorta, Cushing disease, hypercalcemia, brain tumors and carcinoid syndrome are less frequently encountered but if present, can cause treatment resistant hypertension.

Treatment

The principal approach to the treatment of treatment resistant hypertension is to identify and eliminate the cause for treatment resistance. This requires the search for possible exogenous substances, including over the counter medications and herbal remedies and specific investigations to assess the possibility of a secondary form of hypertension. Adherence to medication can be improved by patient education preferably in multidisciplinary approach involving also family members and pharmacists. Simplification of treatment[26] e.g. once daily dosing, reduced number of pills through the use of combination

pills[27], and dated pill containers improve compliance particularly in elderly patients. To improve compliance in the case of perceived side effects can be difficult. First, the possibility that the side effects are caused by another, not the antihypertensive drug that the patient is taking has to be excluded as well as possible interactions. Patients often have a preconceived opinion that certain drugs are causing side effects. Again, patient education, sometimes in group sessions can eliminate the concerns of taking medication. Sometimes, the combination of several antihypertensive drugs, each given at a low ("sub-side effect") dose may be tolerated and blood pressure control be achieved.

Weight loss is paramount for obese patients to regain responsiveness to antihypertensive treatment. It has been shown, that a weight loss of 10 kg. lowers systolic blood pressure by 6 mmHg. and diastolic blood pressure by 4.6 mmHg.[28]. Cessation of excessive alcohol intake has been shown to reduce 24-hour ambulatory systolic pressure by 7.2 mmHg and diastolic pressure by 6.6 mmHg.[29]. In patients with sleep apnea, treatment with continuous positive airway pressure (CPAP) can restore responsiveness to antihypertensive treatment[30].

A rational combination of antihypertensive drugs is important and should include a diuretic since blood pressure lowering per se can lead to some sodium and volume retention which is often the cause for treatment resistance (table 3). In patients with chronic renal failure, the use of a loop diuretic may restore the responsiveness to antihypertensive treatment. Sometimes, centrally acting drugs e.g. clonidine or potent vasodilator drugs e.g. may have to be added in order to achieve treatment response through different additional modes of action. The addition of an aldosterone antagonist e.g. spironolactone[31] or eplerenone[32], a more selective aldosterone antagonis with fewer side effects as well as amiloride[33] has been found to cause an additional significant fall in blood pressure regardless of the plasma aldosterone or renin concentration or the amount of urinary aldosterone excretion[31] but requires the monitoring of serum potassium and renal function.

Table 3. Rational combination of antihypertensive drugs

Combination of: - Angiotensin converting inhibitor and/or angiotensin receptor blocker - Diuretic: thiazide diuretic loop diuretic if creatinine clearance <50ml/min or heart failure - Calcium channel blocker
Addition of: - Beta-blockers - Alpha-blockers (+beta –blocker combination) - Aldosterone antagonist (spironolactone, eplerenone, amiloride) - Clonidine - Hydralazine - Minoxidil - Methyldopa
Combination of a beta-blocker with a non-dihydropyridine calcium channel blocker should be avoided.
Monitoring of renal function and serum potassium in patients on an aldosterone antagonist and/or an angiotensin receptor blocker particularly in patients with diabetes or impaired renal function.
Avoid sudden discontinuation of clonidine (acute withdrawal syndrome) Minoxidil needs concomitant loop diuretic treatment (fluid retention)

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