



RESISTANT HYPERTENSION

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Definition and Prevalence

Hypertension is still a major health problem affecting approximately 30% of the population by the age of 60 years. 10% of the hypertensive patients appear resistant to therapy (1,2). Resistant hypertension is defined as failure of concomitant use of three or more different antihypertensive agents to lower blood pressure to less than 140/90 mmHg (3) in all age groups. Older studies estimated the prevalence of refractory hypertension in tertiary care centers to be between 5 and 18 % (4-9). In a large cohort study Alderman et al. found that only 2.9% were resistant to antihypertensive therapy (10). Recent clinical trials suggest that resistant hypertension is increasingly common. ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack) Study results indicate a higher prevalence. Among 14722 patients above 55 years, 47% remained resistant to therapy 1 year after randomization (11). Similar results (43% resistance) were obtained in the Systolic Hypertension in Europe (Syst-Eur) Study (12). In studies of more complicated patient populations such as LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) Study, which enrolled hypertensive patients with left ventricular hypertrophy, the control rates (26%) were even lower (13). It should be emphasized that these figures overestimate the prevalence of resistant hypertension in the overall hypertensive population since they are limited to older, higher risk patients (14).

Causes and Therapeutic Approaches in Resistant Hypertension

In the clinical setting, systematic evaluation of patients with refractory hypertension is necessary to identify the contributing factors or mechanisms. Yakovlevitch and Black reported suboptimal drug regimen as the most common factor (43%) followed by intolerance to medication (22%), noncompliance (10%) and secondary hypertension (11%). Rates of secondary hypertension reported by Andersson (10%) and Desforges (11%) were also similar (2,4). Before searching for causes of secondary hypertension which involves expensive testing, more common issues like appropriateness of the regimen, possible drug interactions, associated conditions like alcohol or drug use, poor adherence, pseudohypertension, white coat/office hypertension, volume overload, obesity and sleep apnea should be care-

fully investigated. After eliminating these factors hypertension truly refractory to treatment is a rare finding, estimated to affect less than 5% of the general population with hypertension (16). The most common exogenous substances/drugs compromising hypertension control are NSAIDs, alcohol, recreational drugs, oral contraceptives and psychotropic drugs. It should be remembered that there is a wide individual variation in the effect of drugs and that a minority of patients may be particularly sensitive, so that withdrawal from potentially interfering medication enable a better blood pressure control. Patient compliance is undoubtedly the major component of successful blood pressure control and it can only be confirmed by the patient's self report. Lack of blood pressure control has been attributed to poor adherence to the prescribed regimen in approximately 50% of the cases (17,18,19).

Pseudohypertension, suggested to be more common among elderly, is defined as a condition in which the cuff pressure is inappropriately high compared to the intraarterial pressure because of vascular stiffening. Lack of target organ involvement despite high auscultatory blood pressure values or symptoms of hypotension in a patient with apparent resistant hypertension may indicate pseudohypertension. "Osler's maneuver" proposed as a screening method proved to have little predictive value (20,21).

Although "white coat hypertension" (isolated office or clinic hypertension) and "white coat effect" have been defined in early nineties, there are limited studies concerning the incidence among patients with apparent resistant hypertension (22). In a recent study reported by Brown et al. (1) 2 to 3 of every 10 patients with apparent resistant hypertension have controlled BP when assessed by 24-h ambulatory blood pressure monitoring.

Plasma volume expansion, which can be measured using I125 radiolabeled albumin is common in patients with resistant hypertension (23). These patients respond well to diuretics. Population based studies suggest a linear relationship between dietary salt intake and blood pressure (24,25). Excessive sodium can blunt the antihypertensive effects of ACE-inhibitors and diuretics, so that dietary salt restriction should be recommended to all patients with resistant hypertension.

The results of the Framingham Study indicate an association of BMI (>25-30 kg/m²) and treatment

resistance. Each 10% increase in weight is associated with a 6.5 mmHg increase in systolic pressure (26,27). Weight reduction should be recommended to all overweight hypertensive patients. A significant association between hypertension and sleep apnea was also demonstrated (28,29). Recent studies show that sleep apnea is common in patients with resistant hypertension and although the mechanisms are unclear, treatment of sleep apnea with nasal continuous positive airway pressure causes reductions in blood pressure (30,31,32).

After eliminating and reversal of these reversible contributing factors secondary causes should be considered. Recently, stimulated renin profiling, the so called "physiologic tailoring" of management has been suggested in cases of resistant hypertension (33). Recent reports suggest hyperaldosteronism to be the most common secondary cause (8-32%) followed by renal insufficiency and renal artery stenosis (34,35,36). The recognition that the majority of patients do not have low serum potassium levels, which have been a prerequisite for the diagnosis of primary hyperaldosteronism, contributed to the increased prevalence of the

disease (37). In patients with low renin resistant hypertension, screening for aldosteronism is mandatory. Primary hyperaldosteronism responds well to appropriate treatment (surgical or medical). In renovascular disease revascularization preserves renal function but the effect on blood pressure control is limited (38). Renal insufficiency should be treated according to etiology.

Conclusions

"True resistant hypertension" should be diagnosed only after the elimination of the above mentioned contributing factors. It should be remembered that multiple exogenous factors may coexist with a secondary cause. Treatment of resistant hypertension includes elimination of exogenous factors and use of maximum tolerated doses of multiple agents including a long acting diuretic. A recent study by Ouzan et al. showed that spironolactone added to triple or quadruple therapy in patients with resistant hypertension was safe and effective and reduced the number of drugs required significantly. (39). This finding needs to be confirmed by large scale randomized studies.

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