The Challenges of Resistant Hypertension – The Way Out

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INTRODUCTION

It is well recognized that hypertension (HT) is now a major health problem in India.[1] There is paucity of large authentic, epidemiological studies regarding prevalence of hypertension in India. Over the year the WHO cut-off point of BP ≥160/95 mm Hg to label a person as hypertensive (1959) has been modified to ≥140/90 and this vitiates any assessment of trends of hypertension prevalence over the past four decades and a half (45 years).[1] Nevertheless, the metaanalysis of studies from various parts of India has demonstrated that between 1990-2000, the prevalence of hypertension rose from 11.66% to 26.78% in males and from 13.67% to 27.65% in females in urban population.[1] In rural areas the prevalence ranged from 1991 to 1999 ranged between 1.57% to 4.85% in men and between 3.6% to 5.8% in females[1]. There appears to be a steady increase in the prevalence of hypertension over the last 50 years in India and is likely to be similar to that in USA.[1,2] Evidence from clinical practice and from the literature suggest that approximately half of most common chronic disorders are undetected, that half of those detected are not treated, and that half of those treated are not controlled: 'rule of halves'.[3] This 'rule of halves' also holds good for hypertension.[3]

In spite of our increasing knowledge about the genes which influence pathophysiology of hypertension and influence response to pharmacological antihypertensive agents,[4,5] not all hypertensives achieve their desired goal of blood pressure reduction. The Chennai Urban Population Study (CUPS)[6] also has shown that rules of halves is still valid in the Urban South Indian population and it may safely be assumed that the same more or less holds good in other parts of India. In CUPS it was shown that of 279 individuals with hypertension only 104 (37%) were already diagnosed cases of hypertension. Of the 104 known hypertensives only 52 subjects (50%) were under any kind of antihypertensive therapy and of these 52, only 21 (40%) had BP under control.[6] Many of the 21 patients in CUPS might have been given the label of resistant hypertension. We know that altered gene expression in foetus due to maternal malnutrition also "programmes" hypertension, and human genome project has identified candidate genes in human hypertension.[5] But we have yet to utilize this knowledge in treating patients of resistant hypertension. It is being predicted that we can find out salt sensitive patients by identifying which hypertensives have genetically reduced level of ANP (Atrial Natriuretic Protein).[5] Still the problem of resistant HT is very much there.

According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7 Report)[7] even in an advanced and developed country like USA, approximately 30% of adults are still unaware of their hypertension, more than 40% of individual with hypertension are not on treatment and 2/3rd of hypertensive patients are not being controlled to BP level less than 140/90. The situation in our country can be well imagined. A significant proportion of patients in the treated but not well-controlled group are patients of what is known as resistant hypertension. This article will address the challenge of resistant hypertension.

DEFINITION OF RESISTANT HYPERTENSION[7,8]

Resistant hypertension is defined as the failure to achieve goal BP in a patient who is adhering to full dosage of an appropriate three drug-regimen that includes a diuretic.[7,8] The goal BP is ≤140/90 mmHg (according to JNC-7 report). For hypertensives with diabetes mellitus or renal disease, the goal BP is ≤130/80 mm Hg (according to JNC-7 report).[7]

British Hypertension Society guidelines[9] however, have set slightly lower level of BP lowering goal of ≤140/85 mmHg in non-diabetic subjects, and ≤140/80 mmHg in diabetic hypertensives. The Indian Guidelines for Management of Hypertension[10] have kept BP below 130/85 mmHg in young, middle-aged or diabetic subjects and BP below 140/90 mmHg in elderly subjects as goal level of blood pressure reduction.

All these guidelines, however, accept that despite best practice these levels will be difficult to achieve in some hypertensive people.[11]

It is this subset of hypertensives that poses a challenge to treating clinicians. The present review is intended to discuss methods to identify the causes of resistant hypertension and measures to treat such patients.

CAUSES OF RESISTANT HYPERTENSION

The causes of poor BP control are numerous[7,8] (Table 1) . The most likely cause is volume overload either due to excess sodium intake or inadequate diuretic.[7,8,11] In the pathogenesis of hypertension, the environmental factor that has received the

Table 1 : Causes f Resistant Hypertension[7,8]

- **Pseudoresistance**
  - White coat hypertension or office elevations
  - Pseudohypertension in the elderly
- **Drug-related causes:**
  - Non-adherence, inadequate doses
  - Inappropriate combination (tricyclic antidepressants with MAO-inhibitors)
  - Drugs having potential to raise BP
    a. Sympathomimetics in nasal decongestants, appetite suppressants
    b. Caffeine
    c. Herbal drugs (Ginseng), ephedra, ma haung, bitter orange
    d. Oral contraceptives
    e. Adrenal steroids
    f. Non-steroidal anti-inflammatory drugs (including cyclo-oxygenase-2 selective inhibitors)
    g. Carbenoxolone sodium
    h. Erythropoietin, cyclosporin, tacrolimus, sibutramine
- **Associated conditions**
  - Smoking
  - Obesity
  - Sleep apnea
  - Excess alcohol intake (>1ounce/day)
  - Panic attacks
  - Arteritis
- **Secondary hypertension (Identifiable causes of HT)**
  - Obstructive uropathy, chronic kidney disease, polycystic kidneys, renovascular hypertension
  - Coarctation of aorta
  - Cushing's syndrome, chronic corticosteroid therapy
  - Pheochromocytoma, primary hyper-aldosteronism
  - Hypertension associated with pregnancy
  - Hyperthyroidism, hypothyroidism, acromegaly, hypercalcaemia due to any cause

greatest attention is salt intake. But studies have shown that only 60% of hypertensives are particularly responsive to the restriction of sodium intake. Hence salt restriction will not work in the rest 40% hypertensive population.[12] This factor has to be kept in mind while deciding whether further curtailment of salt intake is necessary to reduce the BP. All the same, effect of salt restriction is important as 50% of salt sensitive hypertensives are found to have recognizable causes of hypertension like primary aldosteronism, bilateral renal artery stenosis, renal parenchymal disease and low-renin essential hypertension.[12] While probing the dietary history one has to assess whether the intake of calcium from dairy sources and potassium, from green vegetables is optimal. Epidemiological studies have shown that essential hypertension is more common in people whose diets are deficient in calcium and potassium. The time old conception about influence of excess sodium intake in causing high BP was tested in experimental studies.[13] It was found that genetically salt sensitive rats such as Dahl S and spontaneously hypertensive rats show clear hypertensive responses to a high salt diet. Neural mechanism play an essential role in salt-induced hypertension and recent studies indicate that centrally induced sympathetic hyperactivity actually causes the hypertension. It has been predicted that genetic studies even in human beings would, in future, identify persons with genetically reduced level of atrial natriuretic protein, who will be salt sensitive. Then it will be easier to emphasize on such genetically salt sensitive individuals the importance of restriction of salt.

Yakovlevitch and Black (1991)[14] in a series of 91 patients with resistant hypertension found that the causes were sub-optional drug regimen (mainly inadequate diuretic dosage) in 43%, intolerance to medication in 22%, non-compliance in 10% and secondary hypertension in 11%.[14]

Blood pressure of patients who, by nature and temperament, are averse to taking drugs[15] and of diabetics tend to be more resistant.[15] Lack of compliance is universal problem but is more so in India where the clinicians in hospital and office practice are overburdened and can not or do not find time for educating patients about virtues of continued and prolonged treatment and about dangers of uncontrolled hypertension e.g. stroke, coronary artery disease, renal failure, ocular complication and peripheral vascular disease. Improper BP measurement; can lead to a false perception that patients' BP is not under control.[7,8] In elderly persons whose brachial arteries are heavily calcified or arteriosclerotic and can not be fully compressed, the BP may falsely be found to be high.[7,8] This is known as pseudohypertension. BP may be recorded higher in clinics than the home BP measurement. This is termed as white coat hypertension and is best detected by ambulatory BP measurement.

DIAGNOSIS OF CAUSES OF RESISTANT HYPERTENSION

History

Diet

Patients should be inquired about the amount of common salt in their diet. Many Indian patients have the habit of adding extra salt over and above that used during cooking and to them low salt intake means simply cutting down on that added salt. Pickles form a usual component in meals in many Indian homes and these are heavily salted. This information must be elicited.

Thorough history about diet will also give us information about causes of obesity, which again is a contributory factor in lack of BP control. It is known that established obesity or being overweight is associated with hypertension. Heightened sympathetic nervous system activity, hyperinsulinaemia, insulin resistance and hyperleptinaemia or a combination of these contribute to obesity-related hypertension.[16] Weight loss program should be an essential component of treatment of resistant hypertension.[16]

Method of BP measurement

Patients should be asked about how their BP is being recorded and this will give us a clue to falsely raised BP if standard cuff is being used to measure BP in obese patients. Thorough and meticulous history will assess whether BP measurement is being taken according to standards set by Indian guideline for management of hypertension.[10] The Indian guidelines clearly state that patient should rest for at least five minutes and refrain from smoking or drinking tea or coffee for at least 30 minutes before BP measurement. BP should be measured is supine, sitting and standing posture, specially in elderly subjects to detect postural hypotension. The BP should be measured in both arms

and higher of the two readings should be recognized as the true BP of the patients.

Compliance

One should assess the compliance of the patients. With revolution of information technology in India many educated hypertensive patients get information from internet about the drugs which have been prescribed by their treating doctors. They are scared of the possibilities of side effects like hypokalaemia, dyslipidaemia, rise of their blood sugar and uric acid levels and impotence, hyponatraemia, hypocalcaemia, neutropenia, thrombocytopenia and pancreatitis.[17] Due to apprehensions either such persons stop the drugs or reduce doses drastically. Lack of compliance is a universal phenomenon,[7-9] but it is more so in Indian perspective. There have been interesting studies[18,19] on non-compliance by patients of hypertension. It can now be shown objectively whether the resistant hypertension is due to poor compliance and poor persistence with prescribed antihypertensive drug regimen or due to drug-non-responsiveness.[18] It has been accepted that about 50% of the patients of resistant hypertension are poor compliers, whose response to simple regimens usually proves satisfactory once their compliance with prescribed regimens is corrected. To quote, Urquhart, "Electronic means for compiling ambulatory patients' drug dosing histories have now made it both technically and economically feasible to distinguish clearly between non-compliers and non-responders which, clinical judgment can not do, because it is no better at making this crucial distinction than a coin-toss. With the advent of reliable, economical measurement of patient compliance with prescribed drug dosing regimens, we can probably eliminate most of the compliance problems".[18] Another problem of whether low dose thiazide diuretics and â-blockers should be prescribed as first drugs to improve compliance and persistence with therapy has been addressed by Spence et al.[19] They found that in a Canadian family practice teaching unit, at least 50.8% to 66.7% of patients with hypertension had associated conditions that, according to consensus guidelines are contraindications to â-blocker and diuretics. There is substantial evidence that patients who are taking drugs with less adverse effects, such as angiotensin antagonists [ACE-inhibitors and angiotensin-receptor blockers (ARB)] are more likely to be persistent with therapy, and that persistence with therapy is associated with reduced cost. Hence in treating resistant hypertension substitution of â-blocker and diuretics by newer drugs like ACE-inhibitors, ARBs, calcium channel blockers may yield the desired results, and should no longer be taboo. The problem of non-compliance and non-adherence to therapy are also linked to adverse effects of drugs. To quote Düsing,[20] "Side effects may induce variable compliance and non-persistence by yet another mechanism. Therapy turbulence, i.e., any change in medication, necessitated by adverse effects of earlier therapy is also associated with non-persistence. Therefore, side effects may directly or indirectly (via inducing therapy turbulence) underlie variable compliance and non-persistence".[20] This fact should not be lost sight of while assessing cause of resistant hypertension.

Adequacy of antihypertensive drugs

It should be assessed whether the dosage and frequency of antihypertensive medication are appropriate. It is important to find out whether a diuretic has been incorporated in the drug regimen, as this may be the clue to cause of resistant hypertension.

Hypertension inducing drugs

Detailed history about the concomitant use of medications that are known to push up BP e.g. contraceptive pills, non-steroidal anti-inflammatories including Cox-2 inhibitors, corticosteroids, licorice (carbenoxolone), erythropoietin, cyclosporin, tacrolimus or anti-obesity drugs like sibutramine should be elicited. In younger patients it is important to ask about use of illicit drugs like cocaine, amphetamines etc. It goes without saying that history of excess alcohol consumption and smoking should be elicited. Probing questions may yield information about use of herbal drugs like ginseng and ephedra. Inappropriate combination of drugs like concomitant use of tricycle antidepresive and MAO-inhibitors causes steep rise of BP which will only come down if one of these drugs is stopped.

Sleep apnea

History of snoring, at night and daytime drowsiness especially in obese patients will give a clue to sleep apnea as the cause of resistant hypertension.

Urinary symptoms

One should elicit history of haematuria, nocturia, polyuria, dysuria, hesitancy and urgency to exclude renal causes and obstructive uropathy, as the real aetiology of resistant hypertension.

Intractable pain

Chronic pain hampers control of HTN.

Psychogenic conditions

One should assess whether patient is having history suggestive of anxiety-induced hyperventilation and panic attacks.

White coat hypertension

If a patient complains that his or her home BP is in normal range, this should not be ignored as the high BP recorded in clinic may be due to white-coat-hypertension.

Hyperaldosteronism

History of tetany, episodic muscular weakness without oedema, may give a clue to primary aldosteronism as the underlying cause of resistant hypertension.

Smoking and excessive consumption of alcohol

History of excessive smoking and indulgence in alcohol should be elicited. These lead to ineffectiveness of antihypertensive drugs.

Clinical Examination

Correct BP recording, measurement of waist circumference and palpation of peripheral pulses for atherosclerosis are important steps to know the cause of uncontrolled BP. Palpation for femoral pulses, renal lump and auscultation over abdomen for renal artery bruit will exclude coarctation of aorta, renal hypertension and renovascular hypertension respectively which all may be underlying causes of resistant hypertension. Clinical features of Cushing's syndrome, hypothyroidism and thyrotoxicosis should be looked for. Ophthalmoscopy will detect malignant or accelerated hypertension as cause of resistant hypertension.

Laboratory investigations, radiology and imaging

Urinalysis for sugar, albumin, red cells, pus cells, casts etc. to exclude diabetes mellitus and renal lesion is important. Biochemical evaluation for sugar, urea, creatinine, potassium, serum cortisol, urinary free cortisol and free T_3, free T_4, TSH will detect causes of secondary hypertension like diabetes mellitus, renal hypertension, primary aldosteronism, Cushing's syndrome and thyroid dysfunction as causes of resistant hypertension respectively.

Presence of urine for porphobilinogen will lead to appropriate investigations for acute intermittent porphyria as this may be cause of resistant hypertension. Tests for antinuclear factor and anti-double-stranded-DNA may be done to confirm systemic lupus erythematosus (SLE) as a cause of resistant hypertension, if actinic dermatitis, butterfly erythema, arthralgia and arthritis, lymphadenopathy, hepatosplenomegaly, raised blood urea and creatinine point to a possibility of SLE.

Urological survey including ultrasound for kidney, bladder, residual urine and prostate to exclude obstructive uropathy is essential to detect remediable cause of uncontrolled HT.

Ultrasound and Doppler flowmetry and MR angiography will be helpful in detecting renal artery stenosis and should be later confirmed by captopril renal scintigraphy and digital subtraction angiography.

MANAGEMENT OF RESISTANT HYPERTENSION

Reiteration of low salt intake

Patients should be advised to add only 1 to 1½ teaspoonful of common salt (which comes to about 4-6 gm sodium chloride) to unsalted food after cooking. It is important, though it will reduce BP in only salt-sensitive persons.

Advice about stoppage of certain food

Stoppage of pickles, papads, nimkins, mathrees, potato chips, smoking and stoppage and moderation of alcohol (to 2 ounces of whisky, 10 ounces of wine or 24 ounces of beer) are mandatory.

Antihypertensive drugs

Dosage of diuretics and other hypotensive drugs should be escalated to their recommended maximum. In patients of chronic renal impairment thiazide diuretics should be replaced by loop diuretics like frusemide or torsemide.[7] Patients, in whom diuretics or â-blocker are contraindicated, and are still being used should be put on newer drugs.[19]

Drugs which escalate BP

These as mentioned earlier should be stopped. If stoppage is not possible, then dose of antihypertensive drug should be increased or more drugs from other groups added.

Sleep apnea

It should be diagnosed with help of sleep laboratory, if facilities exist. It should be treated with use of C-PAP (Continuous Positive Airway Pressure) and antiobesity measures should also be instituted.

Anxiolytics

These may be added to treat anxiety-induced hyperventilation and panic attacks.

Identifiable causes

Where possible there should be treated appropriately. If bilateral renal artery stenosis is detected, then ACE-inhibitor or angiotensin receptor blocker should be stopped, and angioplasty with or without stenting should be employed. Trans-aortic renal endarterectomy or renal artery bypass may be taken recourse to, if angioplasty fails.[21]

Surgical treatment or extracorporeal shockwave lithotripsy for renal calculi should be carried out. If hydronephrosis due to PUJ obstruction is there it should be treated surgically. Obstructive uropathy should undergo urological intervention.

Cushing's syndrome and thyroid dysfunction should be treated. Coarctation of aorta should have balloon angioplasty or surgical resection of coarcted site.

ADDRESSING INCREASED CVD-RISK IN RESISTANT HYPERTENSION

The resistant hypertensive patients have been exposed to high level of BP for long. The risk of cardiovascular disease (CVD) beginning at 115/75 mm Hg doubles with each increment of 20/10 mm Hg.[7] The patients of resistant hypertension are at many times higher risk of CVD. Therefore this CVD risk should be addressed at the same time as reduction of BP to goal level. Besides lifestyle modification and three or four antihypertension drugs, there is need of statin and aspirin in such patients, more so if the patient is a diabetic and elderly.[19-21]

ROLE OF ASPIRIN IN RESISTANT HYPERTENSION[22-24]

Aspirin 75 mgm OD should be started in elderly (50 year and above) or/and hypertensive patients with diabetes mellitus after their BP has been brought down to goal level (130/80 in diabetics and patients of renal disease and 140/90 in others) if their 10 years coronary artery disease risk (CAD-risk) is ≥15%, if serum cholesterol is ≥5 mmol/L and if target organ damage (TOD) or clinical cardiovascular disease (CCD) exist. The incidence of CAD and ischaemic stroke is definitely reduced.

ROLE OF STATINS IN RESISTANT HYPERTENSION[22-24]

Statins have been proved to reduce the incidence of coronary events, stroke and all cause mortality and are safe simple and well tolerated, in hypertensives more so in elderlies and/or diabetics. Statins are indicated in resistant hypertensives with diabetes mellitus up to the age of 75 years if serum cholesterol is ≥5 mmol/L and 10 years CAD risk is ≥30% specially if the patient has angina of effort or has history of or is suffering from myocardial infarction. Statins lower blood pressure also and they correct dyslipidaemia that may be found in patients of resistant hypertension.

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