ISOLATED SYSTOLIC HYPERTENSION

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Until the 1980’s the diastolic blood pressure (DBP) was assumed to be the most relevant hemodynamic parameter for prognosis of hypertensive patients. Elevated systolic pressure was considered as an inevitable consequence of aging and many physicians were reluctant to pay credence to the need for therapy of elevated systolic blood pressure. There was a radical change in thinking based on epidemiological studies and reports by insurance companies which led to recognition of elevated systolic blood pressure (SBP). The term isolated systolic hypertension (ISH) has been introduced particularly in elderly subjects, since SBP is known to rise with advancing age; whereas diastolic blood pressure (DBP) usually levels off and tends to decrease in elderly. According to the National Health and Nutrition Examination Survey (NHANES) III, ISH is the most prevalent type of untreated hypertension over 60 years of age. ISH represents a substantial health care problem as the target BP is very difficult to attain by drug therapy.

According to JNC-VI and WHO/ISH guidelines, ISH is now defined as BP >140/<90 mmHg, this criteria is more stringent than older definition of ISH >160/<90.

ETIOLOGY OF ISH

Apart from ISH seen with advancing age, ISH can also be seen in young patients (obese, smokers, low education and socioeconomic status), hyperthyroidism, hyperaldosteronism, renal insufficiency and failure, renal artery stenosis, drug induced (NSAIDS, COX-2 inhibitors, corticosteroids, cyclosporine), herbal remedies, excess alcohol use, obstructive sleep apnoea, anaemia, beriberi, Paget’s disease and cancer (due to release of humoral pressor substances or hypercalcemia).

PATHOPHYSIOLOGY OF ISH

ISH largely reflects progressive structural and functional deterioration of arterial wall involving endothelial dysfunction, atherosclerosis, aortic stiffness and increased wall stress and pulse pressure. According to the hypothesis, atherosclerosis, triggered by vascular endothelial damage and mechanical strain from each stroke volume, plays a central pathophysiological role. Atherosclerosis progressively leads to the replacement of elastin by collagen and other structural proteins and the build of calcium in the arterial wall, and this in turn leads to hypertrophy and fibrosis of arterial smooth muscle. All these factors lead to increased vascular stiffness which results in reduction in arterial compliance and decreased of ‘Windkessel function’ of large arteries.

Renin angiotensin system plays an important role in pathogenesis of arterial stiffness by decreasing elastin content and increasing collagen of arterial wall. Proliferating small muscle cells in the arterial wall results in increased thickness, stiffening, and partial loss of contractility.

CLASSIFICATION OF ISH

ISH is classified as shown in Table 1.

SYMPTOMS AND SIGNS

In most elderly, ISH is asymptomatic. Epistaxis may be a presenting feature. Cardiac dysfunction is indicated by symptoms of coronary artery disease, heart failure, arrhythmias. Stroke, intermittent
claudication due to peripheral arterial disease, aortic aneurysm, aortic dissection, features of hypertensive retinopathy, renal insufficiency or failure may be present. Severe hypertension or an abrupt rise of BP may cause headache, blurred vision or dizziness.

EVALUATION OF ISH

An initial evaluation of ISH should include assessment for other cardiovascular risk factors, end organ damage, identifiable secondary causes of hypertension and potentially contributing lifestyle factors (diet, exercise, alcohol, smoking, body weight, drugs).

Physical examination should include assessment of peripheral pulses, optic fundi, thyroid, heart, lungs, kidney and neurological system. Abdominal and carotid bruit should be carefully looked.

Ambulatory BP Monitoring (ABPM) is of value in elderly patients to confirm the diagnosis of hypertension if clinic BP is more than 140/90 mm Hg (White coat effect), to identify non dippers and to assess response to drugs.

Home BP measurement (HBPM) can be suitable alternative to monitor the response to treatment. The devices are easily available and user friendly.

Investigations for end organ damage should include hematocrit, urine analysis for proteinuria, BUN, serum creatinine, uric acid, electrolytes (sodium, potassium, calcium), blood glucose, lipid profile, thyroid function test, ECG, X-ray chest. Echocardiography, carotid doppler, renal doppler, CT abdomen/ chest, USG abdomen and polysomnography (in obese subjects) may also be required.

ISH AS A RISK FACTOR

The Framingham study and The Multiple Risk Factor Intervention Trial (MRFIT) showed that SBP levels are stronger predictors of cerebrovascular and cardiovascular events than diastolic BP (DBP).

It should be realized that a too low DBP is also dangerous in those with coronary artery disease. DBP below 60 mm Hg may be associated with an increased risk of myocardial infarction and death (J–curve phenomenon). Several intervention studies in ISH have demonstrated beneficial effects of treatment of ISH.

BENEFITS OF TREATMENT OF ISH

Several interventional trials such as STOP-1, STOP-2 and MRC Elderly have clearly demonstrated that treatment of hypertension in elderly is beneficial and protective against stroke and coronary artery disease. In most of these trials, no clear distinction was made between ISH and ordinary hypertension. However a major percentage of elderly hypertensives recruited for such studies showed hemodynamic characteristics of ISH. A few clinical trials have enrolled patients with well defined ISH.

INTERVENTIONS TRIALS CONCERNING ISH

Systolic Hypertension in the Elderly (SHEP) study

Elderly patients with defined ISH were treated with low dose chlorthalidone (with the option to add atenolol or reserpine), in comparison with placebo. Active treatment brought about the following significant beneficial changes / reductions:

- non- fatal stroke – 37%
- nonfatal MI – 33%
- left ventricular failure – 54%

There were obvious trends (although not significant) towards decrease in

- TIAs (-25%)
- Total mortality (-13%)
- Cardiovascular mortality (-20%)
- Cerebrovascular mortality (-29%)
- Coronary mortality (-15%)

In addition, this study has confirmed and emphasised the beneficial effects and safety of low dose diuretics in elderly hypertensives.

Systolic Hypertension in Europe (SYST-EUR) Trial

In large number of ISH patients active treatment with the calcium antagonist nitrendipine (with optional add on enalapril and/or hydrochlorothiazide) was compared with placebo, in a double blind randomized design.

A significant reduction (by 42%) in the incidence of stroke and vascular dementia (by -50%) by nitrendipine treatment was found.

Systolic Hypertension in China (SYST-China) Trial

In large number of ISH patients active treatment with the calcium antagonist nitrendipine (with optional add on enalapril and/or hydrochlorothiazide) was compared with placebo, in a double blind randomized design.

A significant reduction (by 42%) in the incidence of stroke and vascular dementia (by -50%) by nitrendipine treatment was found.

The design of this trial, performed with Chinese ISH patients, was very similar to that of the SYST-EUR study. In the Chinese

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Isolated Systolic Hypertension

patients active treatment with nitrendipine significantly reduced the following endpoint phenomenon:
• total stroke – 38%
• stroke mortality -58%
• all cause mortality -39%
• cardiovascular mortality -39%
• fatal and non-fatal cerebrovascular events -37%

Intervention as a Goal in Hypertension Treatment (INSIGHT) Study

The INSIGHT study was performed in hypertensive patients with at least one additional risk factors such as hyperlipidemia or diabetes mellitus. The study was not deliberately designed to investigate ISH treatment, but it contained a subgroup of patients with defined ISH which were analysed separately.

Treatment consisted of nifedipine (in the GITS form: Adalat-OROS), versus hydrochlorothiazide. This subgroup of patients appeared to be more responsive than those with ‘ordinary’ hypertension to treatment with nifedipine – GITS. Interestingly, in these study patients with ISH whose DBP significantly decreased with increasing therapy were smokers with evidence of atherosclerosis.

Both types of treatment (calcium antagonist vs diuretic) caused a significant and sustained reduction in blood pressure (in particular SBP) and a significant reduction of the relevant endpoint parameters, such as stroke and MI.

Losartan Intervention For Endpoint reduction (LIFE) study

The ISH substudy of LIFE compared Losartan with atenolol and demonstrated that losartan reduced the risk of stroke and CV death to greater degree than atenolol.

Angiotensin II receptor antagonist telmisartan in isolated systolic hypertension (ARAMIS) studies:

Telmisartan (20 – 80 mg) produce significant reduction in SBP
Valsartan in Isolated systolic hypertension (VALISH)

This study showed a significant effect on ISH.

Smaller studies on ISH

ACE inhibitors like lisinopril, Enalpril, Periondopril are also suitable for blood pressure control in ISH patients and favourably influence cardiovascular risk factors.

In conclusion, it appears mandatory and possible to treat ISH and there is sufficient evidence that has demonstrated beneficial effects of this treatment.

MANAGEMENT OF ISOLATED SYSTOLIC HYPERTENSION

The management of ISH should start with lifestyle changes followed by drug therapy.

1. Life style changes:

The lifestyle changes recommended for patients with isolated systolic hypertension are the same as those for patients with other forms of hypertension.

a. Weight reduction: Decrease in body weight decreases the incidence of hypertension and the vice versa is also true, reduction in 1.0kg body weight decreases blood pressure by 1.6/1.3 mmHg. It improves insulin sensitivity, sleep apnoea and the sensitivity to sodium decreases. It is advisable to maintain ideal body weight (BMI 18.5 – 24.9 kg/m²).

b. Dietary sodium restriction: Moderate degrees of sodium restriction to 2.4 gm/day results in SBP reduction by 2 - 8 mm Hg. Indian patients with ISH are more responsive to sodium restriction, because of their lower renin responsiveness. In Indians there is hidden salt in many food items and common practise to consume items (pickle, papad, sausages) which are loaded with sodium.

c. Diet Changes: Role of diet has been proven in DASH (Dietary Approaches to Stop Hypertension), TONE (Trial of Nonpharmacological Interventions in the Elderly), and many more trials. The diet should be rich in fruits, vegetables, low in saturated and total fat and high in fibre content. It causes SBP reduction by 8 -14 mm Hg.

d. Moderation of alcohol: Alcohol abuse is the commonest cause of reversible hypertension. Limit consumption to not more than 2 drinks per day in men and one drink per day in women. It causes SBP reduction by 2 - 4 mm Hg. These are associated with fewer coronary events and strokes in comparison to teetotallers.

f. Avoidance of tobacco: Smoking is prevalent in urban and rural population. It is a significant contributory factor for ISH, along with other detrimental effects on other body systems.

g. Physical exercise: Regular aerobic physical activity such as brisk walking at least 30 minutes daily for most of the days of the week results in SBP reduction by 4 - 9 mm Hg.

h. Stress management: Relaxation techniques, yoga, massage can reduce blood pressure and this can be a part of their treatment.

i. Low caffeine: Discourage excessive consumption of coffee and other caffeine rich products.

These lifestyle changes reduce the blood pressure and
favourably affect other risk factors like obesity, lipid disorders and diabetes.

2. Drug Treatment

General principles of drug therapy:

a. The therapy in ISH should begin with life style changes which may decrease the need of medications.

b. The initial dose of drugs should be as low as possible to achieve the pharmacological effect and gradually increase the dose to attain the target BP.

c. The minimum goal for BP control in ISH is < 140 mm Hg and in patients with diabetes and renal disorder, the goal is <130 mm of Hg.

d. Care should be taken to avoid DBP < 55 mm Hg in older patients with ISH.

e. Avoid orthostatic hypotension in diabetics and in immobile patients.

f. Most of the patients will require more than one drug to achieve target BP control in ISH.

g. Carefully consider all the pre-morbid conditions like diabetes, kidney disease, lung disease, coronary artery disease, prostatomegaly before selecting the agent.

h. Select a drug which can give multiple benefits, add on therapy can be given, if target BP in ISH is not controlled.

Six major classes of antihypertensives which are most useful in ISH:

A. Diuretics
B. Calcium channel blockers
C. Angiotensin Converting Enzyme (ACE) inhibitors
D. Angiotensin Receptor Blockers (ARB’s)
E. Beta adrenoreceptor blockers
F. Alpha adrenoreceptor blockers

A. DIURETICS

The current Joint National Committee guidelines recommend thiazide diuretics as initial drug therapy for most patients with isolated systolic hypertension on basis of their efficacy of reducing blood pressure, cardiovascular complications and their low cost. Thiazide diuretics induce glucose intolerance and hypokalemia resulting in muscle fatigue, weakness, lethargy. The clinical importance of these adverse effects is uncertain. Most of the patients will end up receiving diuretic as a part of their regimen as more than one drug is required to control blood pressure. Diuretics can be combined with most of the other class of antihypertensives. The New 2011 British hypertension guidelines commissioned by the National Institute for Clinical Excellence (NICE) and developed in conjunction with the British Hypertension Society (BHS) highlights the use of thiazide like diuretic, such as chlorthalidone (12.5-25 mg once daily) or indapamide (1.5-2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide, if there is high risk of heart failure. In presence of elevated serum creatinine levels (S Cr > 2) the diuretic of choice would be Furosemide, Toresemide or Metolazone.

B. CALCIUM CHANNEL BLOCKERS

This group of drugs is effective in hypertensive diabetics, a combination very commonly seen in clinical practice. A unique character of CCBs is that its antihypertensive efficacy is not blunted by non-steroidal anti-inflammatory agents (NSAIDs) which can elevate BP by 3-6 mmHg. The commonly seen side effects of CCBs are leg edema & constipation. Lercanidipine, a newer long-acting dihydropyridine is promising to have lesser incidence of leg oedema and has associated antiatherogenic properties. Its antihypertensive efficacy and tolerability has been established in recent ELYPSE trial.

C. ANGIOTENSIVE CONVERTING ENZYME (ACE) INHIBITORS

Hypertensives with high renin are more prone to cardiovascular events and show maximum benefit with ACE inhibitor therapy. The ACE inhibitor should be started in low dose and to be increased gradually to prevent first dose hypotension. ACEI are considered standard therapy in hypertension with renal disorders, diabetes, diabetic nephropathy and LV dysfunction. ACE inhibitors are preferred in elderly because of end organ protection in cardiac and renal patients. The ACE inhibitors often induce a persistent dry cough and in rare instances, angioedema.

D. ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)

ARBs may be especially useful in treating ISH. All the ARBs are potent in reducing SBP levels as shown by various clinical trials, and have a class effect.

This group of drugs was initially introduced as an alternative to ACEI, for those who are intolerant to them due to severe dry cough. The ISH substudy of LIFE demonstrated for the first time in patients with ISH that losartan confers more CV benefits over atenolol at the same level of BP control. The ARBs are used in the renal
diseases, proteinuria, and heart failure. The compelling contraindication is renovascular disease.

A remarkable feature of ARBs is safety and tolerability profile. The combinations of ARBs and ACEI have additive effect in lowering BP and proteinuria.

E. BETA ADRENORECEPTOR BLOCKERS

Beta-blockers are effective in reducing blood pressure in ISH. The use of beta-blockers as first line therapy for elderly patients has been controversial; a meta analysis of trials for hypertension showed a 16% higher incidence of stroke among patients treated with atenolol as compared to other antihypertensives. It may be due to small reductions in blood pressure. A recent study showed that ISH is less responsive to beta blockers as compared to patients with essential hypertension. The rate lowering effects of beta blockers may result in increase in systolic and pulse pressure. The use should limit to those with compelling indications such as coronary artery disease, myocardial infarction, congestive failure or certain arrhythmias, young patients, women with child bearing potential. Beta blockers are associated with a number of chronic adverse effects like lethargy, fatigue, muscle weakness, cold extremities and impotence in men.

F. ALPHA ADRENORECEPTOR BLOCKERS

Selective alpha blockers like Doxazocin, Prazosin have been shown to be effective agents as monotherapy. Men with ISH and prostatic hyperplasia may obtain dual benefit from these drugs. Postural hypotension and heart failure are known side effects with them.

The centrally acting agents such as clonidine and methyldopa result in dry mouth, sedation and rebound hypertension. Selective Imidazoline (Type I) agonists, such as moxonidine and rilmenilidene are reasonably effective and well tolerated.

NEWER ATTEMPTS TO TREAT ISH:

It would be desirable to find new antihypertensive agents which selectively decrease SBP without reducing DBP. Some of these drugs are:

1. Nitrates as NO generator may be considered as a potential new agent to treat ISH. Isosorbide dinitrate took eight weeks of treatment to show this effect on SBP. Transdermal nitroglycerine and molsidomine demonstrated similar effect.

2. Spironolactone, an aldosterone antagonist is weak potassium sparing diuretic which also inhibit the enhanced formation of collagen and vascular fibrosis provoked by aldosterone. Spironolactone can control the arterial stiffness which is the basis of ISH.

3. Eplerenone, a newer aldosterone antagonist results in very low incidence of gynaecomastia.

4. Bosentan, an endothelin receptor antagonist demonstrated BP-lowering effects. Drug toxicity (i.e., teratogenicity, testicular atrophy, and hepatotoxicity) has largely limited the use of this drug, but new agents are in the pipeline.

5. Aliskiren, recently released renin inhibitor, demonstrated antihypertensive efficacy similar to that of currently available ACE inhibitors and ARBs. The advantage of aliskiren is that it suppresses renin activity, unlike ACE inhibitors and ARBs, which can lead to a reactive rise in plasma renin activity.

All these agents require larger studies and investigations for their widespread use in ISH.

ISH IN THE YOUNG

Little is known about isolated systolic hypertension (ISH) in younger adults. ISH among young adults is increasing in prevalence, and is more common than systolic/diastolic hypertension. Obesity, smoking, and low socioeconomic status appear to be important determinants of ISH among young adults and have all increased over the last decade.

The onset of hypertension during early adulthood warrants particular concern as even slight elevations in SBP during early adulthood increase one’s risk for further cardiovascular disease morbidity in later life.

Increased blood viscosity is associated with obesity and might, by increasing the rheological component of peripheral resistance, contribute to obesity-associated changes in arterial blood pressure. Body fat has been shown to be a strong predictor of aortic stiffness in both young and older adults, which may account for the isolated elevation in SBP among obese young adults.

ISH IN HYPERTHYROIDISM

The secondary causes of isolated systolic hypertension include anaemia, aortic insufficiency, Paget’s disease, beriberi, and hyperthyroidism. They all share a common mechanism of an increase in cardiac output.

The prevalence of ISH in thyrotoxicosis is 20–30%. Triiodothyronine (T3) is the active form of thyroid hormone. In hyperthyroidism, T3 dilates resistance arterioles, reducing systemic vascular resistance, which stimulates renin release and sodium reabsorption, resulting in an expansion of blood volume by 5.5% and an increase in venous return to the heart. Erythropoietin stimulation also contributes to blood volume. Heart rate and cardiac contractility are also changed with hyperthyroidism. Cardiac output is increased by >1 L/min.

The net effect of these hemodynamic changes is a rise in
SBP and a widening of pulse pressure. Arterial stiffness is increased.  

Treatment with antithyroid drugs narrows the pulse pressure, decreases heart rate, reduces cardiac output and improves the ISH.

REFERENCES