Isolated Systolic Hypertension

16

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Key Points

- ISH is diagnosed when systolic blood pressure is more than 140 mmHg with a normal or low diastolic pressure (less than 90 mmHg).
- Prevalence of ISH increases with age, and it is one of the special problems in hypertension among geriatric population.
- Contrary to traditional thinking, systolic hypertension is a strong predictor of cardiovascular morbidity and mortality.
- Increased arterial stiffness resulting in augmented reflection of the pulse wave is the major pathophysiological mechanism in ISH along with functional changes like endothelial dysfunction, enhanced sympathetic tone, and abnormal sodium hemostasis.
- Management of ISH can be a challenge, and drugs which reduce the augmentation index play a pivotal role in refractory cases.

Case Study

Mr. JS is an 84-year-old gentleman diagnosed with systemic hypertension. He is physically active and does moderate physical exercise for 45 min daily and maintains a healthy body weight. He has mild type 2 diabetes which is being managed with met for min 500 mg daily. He had suffered a minor stroke in the past from which he has recovered completely without any residual neurological damage. His blood pressure has been a challenge to his GP and was very difficult to control with three antihypertensive drugs, viz., atenolol 50 mg, amlodipine 10 mg, and lisinopril 10 mg.

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During his last clinic visit, his pulse rate was 55 beats/min, BP 170/75 mmHg, and normal cardiac physical findings. ECG showed sinus rhythm and features of left ventricular hypertrophy (LVH). Echocardiogram results reported mild concentric LVH with normal LV function. Blood chemistry was normal with regard to renal function, electrolyte status, liver functions, and blood sugar levels including HbA1C, but serum uric acid levels were at upper limits of normal.

How to manage Mr. JS' hypertension?

16.1 Isolated Systolic Hypertension

Definition: According to WHO/ISH guidelines and the Sixth Joint National Committee on Hypertension report, ISH is diagnosed when the systolic BP is ≥140 mmHg and diastolic BP (DBP) < 90 mmHg.

Population-based studies have demonstrated age-related increase in both SBP and DBP up to the sixth decade. In elderly population, there is a slow decrease in DBP in contrast to SBP [1, 2]. Traditionally it was thought that elevated diastolic BP, not the systolic BP, is the major risk factor for increased vascular morbidity and mortality. DBP was the main target of any antihypertensive drug therapy. However retrospective as well as prospective epidemiological studies have demonstrated beyond any reasonable doubt that SBP is an important risk marker irrespective of the DBP.

16.2 Pathophysiology

16.2.1 Genesis of Pulse Wave

An understanding of the genesis of the pulse wave is necessary to comprehend the pathogenesis of isolated systolic hypertension. The pulse wave is generated by left ventricular contraction and is propagated throughout the arterial vascular bed. The normal pulse wave consists of an upstroke, peak, and a descending limb. The first upward excursion is the rapid upstroke or percussion wave. The percussion wave is followed by the sharp dicrotic notch which is caused by aortic valve closure at the end of systole. The dicrotic notch is followed by the dicrotic wave, which is the second upward component which is late in systole. The dicrotic notch and dicrotic waves are better recorded in central arteries and less discernible toward the periphery. The dicrotic wave is due to the reflection of the incident wave from the arterial bed. In normal vasculature, the reflection is small and is in diastole, and therefore, no summation with the first wave happens in a normal vasculature (Figs. 16.1 and 16.2).

Age-related decrease (structural and functional) in the arterial compliance is the major pathophysiological mechanism in development of ISH. These changes affect mainly the intima and media [3–5]. Functional properties as well as anatomy of the large vessels are altered due to changes in collagen, ground substance, as well as extracellular protein matrix. The amount of elastin on the arterial walls decrease with

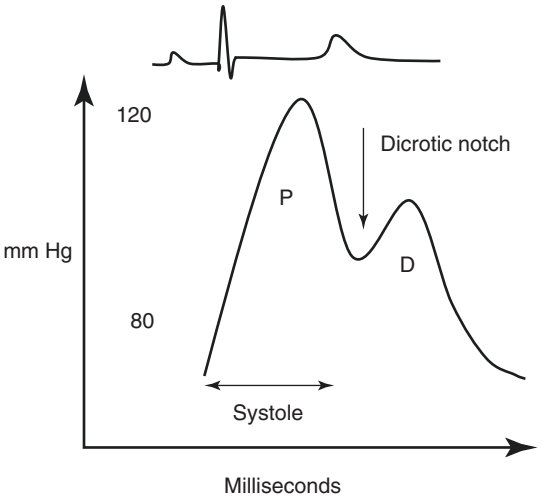

Fig. 16.1 Pulse wave form from healthy vasculature. *P* percussion wave, *D* dicrotic wave. The *arrow* indicates the dicrotic notch. The reflected wave or dicrotic wave is small and is in diastole, and there is no summation with the percussion wave

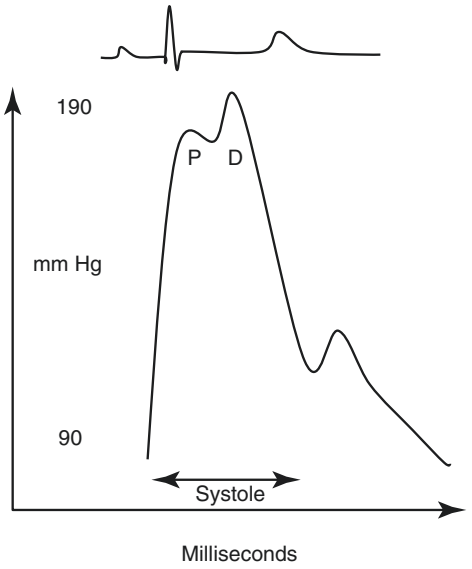

Fig. 16.2 Pulse wave form in ISH. Dicrotic wave is earlier and in systole because of accelerated reflection, and there is summation with the first wave. There is augmentation of the systolic pressure because of this summation effect

aging, which result in fragmented and poorly demarcated media. Atherosclerotic process and calcification of the media also contribute to increasing stiffness and reduced elasticity of the arterial walls. Through the porous internal elastic lamina, undifferentiated smooth muscle cells migrate to the intima and proliferate there, laying down collagen contributing to fibrosis of the intima. This in turn results in increase in arterial wall stiffness. The end result of these processes is decrease in lumen-to-wall ratio and overall cross-sectional luminal area and decrease in arterial stiffness. Changes are predominantly seen in elastic arteries like aorta and larger arteries [6, 7].

These changes cause increase in pulse wave velocity. This results in early return of reflected pressure waves from peripheral reflecting sites, a summation with the first component and an increase in systolic pressure [8]. The widening of the arterial pulse pressure caused by the reflected component is expressed as the "augmentation index" (AIx) [9]. It also causes increased wall stress, augments the processes involved in atherosclerosis, and also predisposes to development of left ventricular hypertrophy (LVH).

16.3 Functional Changes

There is an increase in sympathetic tone with aging. Circulating nor adrenaline levels are high, which is likely due to a lowered beta receptor sensitivity and decreased baroreceptor sensitivity. A preserved alpha-receptor activity in elderly population with an increased sympathetic tone will result in a state of generalized vasoconstriction and increased vasomotor tone [10].

16.3.1 Endothelial Dysfunction

Cardiovascular risk factors especially diabetes, renal dysfunction, dyslipidemia result in endothelial dysfunction as evident by impaired nitric oxide (NO) production and loss of vasodilator tone. The resultant tonic vasoconstrictive state of the vascular bed results in an amplified reflective wave and systolic augmentation [11–14].

16.3.2 Volume Status and Sodium Hemostasis

Elderly hypertensives are more sensitive to the volume perturbations secondary to sodium intake. There is an increased sensitivity for salt-induced inhibition of endogenous NO production, which can increase the vasoconstrictor tone [15, 16].

16.4 Epidemiology of ISH

There is a clear linear relationship between age and ISH. The prevalence of ISH is 0.8% in people < 50 years of age and up to 23.6% in persons 80 years of age [17, 18]. Prevalence is more in females and African Americans compared to Caucasians [17, 18]. However, these data are from studies which defined ISH as systolic BP > 160 mmHg and diastolic BP < 90 mmHg as per the WHO guidelines [19, 20]. As indicated earlier, the diagnostic criteria has been redefined with SBP > 140 mmHg and DBP < 90 mmHg by the Sixth Joint National Committee on hypertension [21].

16.5 Morbidity and Mortality of ISH

The deleterious effects of ISH were first demonstrated in 1959 in the *Build and Blood Pressure Study*. The relation between SBP and mortality was demonstrated in the retrospective analysis of insurance company data. A close relation between mortality and high systolic pressures was demonstrated, which was age independent [22]. This data from retrospective analysis was later confirmed by prospective studies. Data from Multiple Risk factor Intervention Trial (MRFIT) and the US Hypertension Detection and Follow-Up Program confirmed the association between increase in SBP and cardiovascular risk [23, 24]. Every 1 mm increase in SBP has been shown to increase the cardiovascular mortality by 1% in multiple regression analysis. Framingham study data also reiterated the cardiovascular morbidity and mortality. There was a twofold increase in the risk of nonfatal MI and threefold increase in the risk of strokes with ISH in Framingham population [11, 12].

Data from MRFIT trial have confirmed the fact that systolic BP elevation is a more important risk factor for cardiovascular events than diastolic BP.

16.6 Modification of Cardiovascular Complications by Treatment

Table 16.1 summarizes the results of three major randomized placebo-controlled trials in ISH management. Undoubtedly treatment of ISH resulted in significant reduction in cardiovascular morbidity and mortality in treated group [25–27].

Table 16.1 Randomized trials in management of ISH

Study	No. of patients	Age group	Enrollment BP (mean)	Drugs	F/U (years)	Mean BP reduction (S/D)	End point reduction
MRC	4396	65–74	183/91	Diuretic/ atenolol	5	−20/−10	25% stroke 19% cardiac
SHEP	4736	>60	170/77	Diuretic/ atenolol	4.5	11–14/3–4	36% stroke 27% MI(NS)
SYST-EUR	6403		160–219/95	Nitrendipine/ enalapril/ diuretic	2	23/7	42% fatal stroke 44% nonfatal stroke 26% fatal/ nonfatal cardiac events

16.7 Management of ISH

The diagnosis should be confirmed by at least three different BP measurements. Attention must be paid to detect any evidence of postural hypotension. Rare and potentially curable secondary causes like aortic insufficiency, thyrotoxicosis, anemia, beriberi, arteriovenous fistulae, and Paget's disease of the bone should be eliminated before making a diagnosis of ISH. Ambulatory BP monitoring is advised in suspected cases of white coat hypertension and in cases demonstrating significant variability in BP recordings.

16.8 Non-pharmacological Management

These include weight reduction, physical activity, restriction of dietary sodium, and moderation of alcohol intake. Low-sodium diet (in the range of 60–90 mmol/day) had appreciable favorable effects on systolic BP in patients with ISH. Reduced dietary sodium also was associated with reduced arterial stiffness and reduction in systolic BP [28–30].

Effect of physical exercise on elderly patients needs further studies, as the current data is inconclusive. Favorable effect of significant lowering of SBP has been noted in a study done in 109 elderly hypertensives, half of them being ISH. SBP was found significantly lower among those who moved more than 5 h a day compared to those with lesser mobility [31]. However, another study did not demonstrate a significant change in arterial stiffness with moderate-intensity exercise for 8 weeks [32]. These lifestyle changes alone may be necessary in mild cases of ISH. These should be continued along with drug therapy in more severe cases of ISH. Drug therapy is indicated in cases with SBP $\geq$ 160 mmHg in spite of lifestyle changes. Threshold to start drug therapy should be lower, even if the BP is between 140 and 160 mmHg in patients with comorbid conditions like diabetes, coronary artery disease, and features of end-organ damage like left ventricular hypertrophy.

16.9 Selection of Antihypertensive Drug in ISH

Most antihypertensives used in treating young hypertensives can be used in managing elderly with ISH. However, there are some special considerations to be made while treating this patient population. Excessive reduction in blood pressure could result in orthostatic hypotension and increase the risk of falls. To avoid this problem, drug therapy should be started at the lowest dose and carefully titrated up to get the target blood pressure level which is typically a systolic BP of $\leq$140 mmHg. In fact antihypertensive therapy has been found to improve the clinical outcomes in patients up the age of 80 years in spite of the risk of postural hypotension. Concomitant reduction in diastolic blood pressure might compromise coronary perfusion especially if there is atherosclerotic narrowing of coronary arteries. A lowered coronary perfusion pressure coupled with left ventricular hypertrophy and

Table 16.2 ISH therapy based on pathophysiological mechanisms

Drug class	Pathophysiological target	Desired change	Side effects
Diuretics	Sodium sensitivity, blood volume	Reduced systolic BP, reduced sodium sensitivity of vasculature	Metabolic: hyperuricemia, worsening renal dysfunction, diabetes
CCB: non-DHP type	Arterial stiffness, wave reflection	Vasodilatation, smooth muscle relaxation, reduced reflection, improved AIx	Peripheral edema
ACEI/AT II blockers	Arterial stiffness, wave reflection	Vasodilatation, smooth muscle relaxation, reduced reflection, improved AIx	Cough (ACEI) angioedema
Nitrates	Arterial stiffness, wave reflection	Vasodilatation, smooth muscle relaxation, reduced reflection, improved AIx	Tolerance
Beta-blockers	Afterload/forward pulse velocity	Reduction in forward pulse velocity/reduction in afterload	No mortality reduction. Diabetes

concomitant increased demands might result in worsening of myocardial demand ischemia.

The pathophysiological mechanisms of ISH would guide the practitioner while choosing the antihypertensive drugs. Selection of the drugs should be individualized based on the presence of comorbid conditions.

Table 16.2 summarizes targeted therapy for ISH based on pathophysiological mechanisms.

16.10 Selection of Antihypertensive Drugs Based on the Pathophysiological Mechanism

While planning the drug therapy, every attempt should be made to select a program to match the pathophysiology in the patient group. It has been demonstrated that drugs that decrease the wave reflection and augmentation index (AIx) are more effective in selectively lowering the systolic BP (e.g., nitrates) than those that have little effect on dicrotic wave reflection and Aix (e.g., beta-blockers) [8, 9, 33].

In a head-to-head comparison of the four major classes of antihypertensives (beta-blockers, calcium channel blockers, ACE inhibitors and diuretics), it was found that the beta-blockers had significantly lower effect on AIx than the other three drug classes: nine diuretics, calcium channel blockers, and ACE inhibitors [34]. These three classes of medications were compared in the ALLHAT trial and have shown comparable efficacy [35]. Two studies have shown thiazide diuretic-based treatment effective in ISH [36, 37]. Indapamide and chlorthalidone were used in these studies, respectively.

A diuretic-based therapy has been suggested in patients with ISH; however, long-term renal and metabolic effects of diuretics should be considered in patients with comorbidities like diabetes, even though the trial of chlorthalidone in ISH has demonstrated improved long-term outcomes in ISH cases. Patients who developed diabetes on chlorthalidone also had a better prognosis than those with preexisting diabetes [37].

16.11 Other Antihypertensive Drugs in ISH

Based on the results of SHEP and SYST-EUR studies, the JNC VI recommended a combination of beta-blockers and diuretics with a target BP < 140/90 mmHg in ISH patients (130/85 in diabetics). Further evidence of the favorable effects of BP reduction below 140 mmHg emerged after JNC VI from ALLHAT trial. Even though ALLHAT showed similar efficacy in reducing clinically significant end points, a meta-analysis of published trials showed a trend for CCBs to be superior to diuretics/beta blockers in reducing stroke and conversely diuretics/beta-blockers and ACEI in reducing heart failure compared to CCBs [38].

Beta-blockers have lost their charm in treating ISH as they were found inferior in preventing stroke compared to other antihypertensive agents [39, 40]. Based on these results from the LIFE trial and ASCOT trial, it has been suggested that beta-blockers should not be used as primary treatment of hypertension.

A substudy of ASCOT-BPLA named as CAFÉ study has examined the hemodynamic effects of two treatment arms. Atenolol ± thiazide therapy was compared to amlodipine ± perindopril arm. In spite of comparable brachial BP reduction, the central aortic pressures and pulse wave augmentation were significantly less with the latter arm thus confirming the importance of reflected waves and augmentation index pathophysiological basis of ISH and associated complications. Agents decreasing the wave reflectance may thus be associated with better clinical outcomes apart from lowering the BP.

Not infrequently, patients already on standard antihypertensive drugs exhibit ISH. Adjuvant therapy with nitrates has been shown to reduce the AIx and systolic hypertension in these cases [13].

Alpha-blockers and central sympatholytics are not suitable for these patients due to their propensity to induce postural hypotension. Per se beta-blockers are not recommended unless there are other indications like heart failure, arrhythmias, or coronary artery disease. Nitrates are valuable add on to those who are not responding to multiple antihypertensives, especially in those with high pulse pressure.

Selection of antihypertensive drugs in ISH thus should be individualized depending on patient's medical history, preexisting medical therapy, and past experiences with individual medications. Thiazide diuretics are a good choice to start with except for those with diabetes, hyperuricemia, and renal impairment. Vasodilators like non-DHP calcium channel blockers and ACE inhibitors/ARBs are also useful in patients especially those who are diabetics.

Conclusions

Isolated systolic hypertension is a major risk factor for cardiovascular morbidity and mortality. The prevalence of ISH increases with increasing age, upto 23% of hypertensives in elderly population have ISH. Contrary to previous concepts, elevated systolic pressures are more deleterious than diastolic hypertension. The pathophysiology of ISH is related to increase in arterial stiffness and pulse wave reflection. These in turn are related to endothelial dysfunction and sodium hypersensitivity. Principles of pharmacotherapy should therefore address these mechanisms. Diuretics and vasodilators specifically non-DHP calcium channel blockers and ACE inhibitors are the mainstay of treatment. Drugs, which reduce the wave reflection and AIx, are especially useful in lowering the blood pressure as well as reducing the cardiovascular/morbidity and mortality in these cases.

Case Continued

Mr. JS depicts a typical scenario of ISH. He is already on near maximal doses of amlodipine and ACEI, and atenolol is one drug which can be increased. However, his heart rate is in bradycardia range, and any further increase in beta-blocker dosage could result in worsening of bradycardia. Diuretic therapy is a choice, but high normal levels of uric acid needs close monitoring. Among the diuretics, indapamide is the most metabolically neutral drug, at the expense of lower potency compared to other thiazides like hydrochlorothiazide or chlorthalidone.

Given these comorbidities, a long-acting nitrate like extended release isosorbide mononitrate (ISMN) which has a favorable effect on AIx can be a drug of choice for managing the ISH of Mr. JS.

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