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Isolated Systolic Hypertension

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The association between hypertension and a "hardening" of the pulse and apoplexy has been recognized for hundreds of years. The major problem in elderly people is isolated systolic hypertension (ISH), defined as a raised systolic pressure but normal diastolic pressure. It affects around half of people aged over 60 years[1]. Originally, because isolated systolic hypertension was so common it was considered part of ageing and, like essential hypertension, benign. However, there is now compelling evidence from cross sectional, longitudinal, and randomized controlled trials that show that isolated systolic hypertension confers a substantial cardiovascular risk[2,3]. Despite this, it remains under-diagnosed and largely untreated[4]. The roots of this lie in a century of over-reliance on the importance of diastolic pressure and largely unjustified concerns about the potential adverse consequences of treating systolic pressure.

INTRODUCTION: WHAT IS ISH?

Isolated systolic hypertension (ISH) is defined as elevated systolic blood pressure (SBP) in conjunction with normal diastolic blood pressure (<90 mmHg). Previously, systolic pressure of more than 160 mmHg was classified as ISH, and pressure between 140 and 160 mm Hg was classified as borderline ISH. In 1993 the definition of ISH was changed to any systolic blood pressure above 140 mmHg together with diastolic blood pressure (DBP) below 90 mmHg[5]. ISH is characterized by an increased pulse pressure, defined as the difference between the systolic and diastolic blood pressures.

Hypertension is present in more than half of all persons over 60 years of age, regardless of race[1]. The majority of hypertensive patients in this age-group have ISH[6,7]. Its prevalence increases with age, from about 5% of persons aged 60 years to almost 25% of those aged 80 years[8], and is higher in elderly women than in elderly men[9].

ETIOPATHOGENESIS OF ISH

Etiology

Many believe ISH to be a natural consequence of aging. However, no age-related increase in blood pressure is seen in relatively primitive societies whose members maintain lean body mass and are physically active. Factors that may play a role in the high prevalence of ISH include:

- Increased body fat,
- Sedentary lifestyle,
- Increased sodium intake[7],
- Smoking,
- Diabetes, and
- Being a Caucasian male or an African American.

Pathogenesis

One of the most important factors in the development of ISH is believed to be a loss of elasticity, and therefore of distensibility, of the aorta and peripheral arteries. Thus systemic arterial compliance is significantly reduced. This decrease in compliance results in higher systolic pressures as the large vessels become less able to reduce the pressure generated by the left ventricle by means of distension. However, while increases in peripheral resistance will cause elevations in diastolic blood pressures, the loss of large-vessel elasticity does the opposite. These counteracting forces may keep the

diastolic pressure normal in the setting of an increasing systolic pressure.

Histopathologic examination of the aorta of an elderly person typically reveals thickening of the aorta and media due to the accumulation of collagenous fibers, as well as calcium deposition[10].

Increased cardiac output may play a role in ISH[11]. In addition, elderly hypertensive patients tend to have relatively low plasma volume and relatively low levels of renin and aldosterone. Renal excretion of salt tends to be decreased in these patients, and this probably accounts for their relatively greater salt sensitivity compared with their younger counterparts[12]. Decreased calcium levels resulting from increased calciuria and poor dietary intake may also increase peripheral resistance, leading to hypertension.

RISKS ASSOCIATED WITH ISH

A common misconception among patients and some practitioners is that elevated diastolic blood pressure is more important than elevated systolic pressure. This misconception most likely stems from studies on hypertension done in the 1960s and 1970s in which diastolic blood pressure was used as a measure of the efficacy of treatment. In fact, elevated systolic blood pressure has consistently been shown to be a better predictor of cardiovascular events. All the recent studies have established that ISH is associated with a significantly increased risk of stroke, myocardial infarction[13], congestive cardiac failure and end stage renal disease[14]. ISH is also associated with a significantly increased risk of overall mortality[15]. The continued reliance solely on diastolic blood pressure readings is puzzling, given the abundant data revealing ISH to be a major cause of morbidity and mortality.

CLINICAL TRIALS

Although more emphasis has been placed on the morbidity and mortality of ISH in recent years, evidence from clinical trials clearly shows that treatment of ISH reduces all the major adverse outcomes.

The SHEP Trial

The Systolic Hypertension in the Elderly Program (SHEP) was the first large-scale trial to document a benefit from treatment of ISH. The 4,736 patients enrolled in this double-blind, randomized, placebo-controlled study were 60 years of age or older. Participants received stepped-care treatment with chlorthalidone, and atenolol was added to the regimen if the target blood pressure was not achieved with chlorthalidone alone. The goal was to reduce systolic pressure to less than 160 mmHg in those with initial readings of more than 180 mmHg and to reduce the systolic pressure by 20 mmHg in those with initial readings between 160 and 180 mmHg. The primary end point was the number of fatal and nonfatal strokes in patients receiving treatment versus those receiving placebo. Secondary end points were cardiac events and overall mortality in these two groups.

Over a 5-year follow-up period, the SHEP trial showed an average systolic blood pressure of 155 mmHg in patients taking placebo and 143 mmHg in patients receiving medication. The overall results were very impressive. The number of strokes was reduced by 36% in the group receiving medication compared with the group receiving placebo. Analysis of secondary end points showed nonfatal myocardial infarctions plus death from cardiac causes to have been reduced by 27% and major cardiovascular events by 32%. The incidence of congestive heart failure was cut in half by treatment with medication. The 13% reduction in all-cause mortality among patients receiving medication did not reach statistical significance[16].

The Syst-Eur Trial

The Systolic Hypertension in Europe (Syst-Eur) trial was conducted about the same time as the SHEP study, but results were published later. The 4,695 patients recruited for the study were over 60 years of age and had systolic pressures between 160 and 219 mmHg and diastolic pressures below 95 mmHg. Patients were randomly selected to receive the long-acting dihydropyridine calcium channel blocker nitrendipine or a placebo. If blood pressure was not optimally controlled, enalapril, hydrochlorothiazide, or both were added.

Over a 2-year follow-up period, patients receiving treatment had their systolic blood pressures lowered by an average of 10 mmHg over the placebo group. The primary end point was fatal or nonfatal stroke. Active treatment reduced the number of total strokes by 42%, nonfatal strokes by 44%, and cardiac events by 26%. As in the SHEP study, total mortality was not reduced significantly by active treatment[17,18].

The STONE Study

The Shanghai Trial of Nifedipine in the Elderly (STONE) was a study of the effects of long-acting nifedipine in elderly hypertensive patients aged 60 to 79 years. Here again, results showed medication to be superior to placebo. The risk of any cardiac or vascular

event was reduced by 59% in the treatment group, mainly owing to a decreased risk of stroke or severe arrhythmia[19].

IMPLICATIONS OF CLINICAL TRIALS

The SHEP, Syst-Eur and STONE trials provide strong evidence that treating ISH can significantly reduce the incidence of stroke, cardiac events, and congestive heart failure. Analysis of the Syst-Eur data indicates that for every 1,000 patients treated for 5 years, 29 strokes and 53 major cardiac events will be averted[18]. This may represent an underestimate of the benefit of treatment, because the analysis includes patients who did not have blood pressure lowered to target goals with active treatment.

EVALUATION OF THE PATIENT

Despite its sizable impact on morbidity and mortality, hypertension is often clinically silent. Cases of ISH require careful attention to patient history, accurate assessment of blood pressure, and laboratory tests to identify concomitant medical problems.

History

The evaluation of a patient with ISH begins with a complete history. Details about the duration and severity of the hypertension should be elicited. Sudden onset of severe hypertension raises the suspicion of a secondary form of hypertension. Information about concomitant medical conditions must be obtained. Patients with a history of cardiac, renal, or vascular disease should have their blood pressure more aggressively controlled than patients without these conditions. Questions about dietary habits, alcohol consumption, tobacco use, and level of physical activity should be asked.

Details should be obtained about the medications that have been tried in the past, with particular attention to their side effects and efficacy in controlling blood pressure. Current medications, including over-the-counter preparations, must be thoroughly reviewed, remembering that elderly patients in many cases are taking multiple agents. Medications such as non-steroidal anti-inflammatory drugs (NSAIDs) can decrease the efficacy of many antihypertensives[20].

Physical Examination

Precise measurement of blood pressure is essential, as there are many potential sources of error. The patient should be seated and comfortable. All outer garments must be removed from the arms. Use of the proper-sized cuff is essential, because one that is too small can cause falsely elevated blood pressure readings. The arms should be well supported, and measurements should be taken in both arms.

Blood pressure should be measured with the patient in both seated and standing positions. Elderly patients are at increased risk of orthostatic hypotension. Patients should be in a standing position for at least 1 minute, and preferably several minutes, before the measurement is taken.

A funduscopic examination should be performed to assess for arteriovenous nicking, a sign of long-standing hypertension. Malignant hypertension may be characterized by papilledema. Palpation may reveal a displaced apical impulse, indicative of left ventricular dilatation. A sustained apical impulse may indicate left ventricular hypertrophy.

Auscultation should focus on listening for an S_4 or any murmurs indicative of coexisting valvular disease. Abdominal examination may reveal an enlarged and pulsatile aorta, which may indicate an abdominal aneurysm. A bruit that lateralizes to one side of the abdomen should raise suspicion for renal arterial stenosis. Femoral and peripheral pulses should be palpated to assess for vascular disease.

Laboratory Analysis

Laboratory tests should focus on assessment for concomitant medical problems as well as end-organ damage. A serum chemistry profile should be ordered to determine whether diabetes, renal disease, or hypokalemia is present. Chronic renal disease is the most common cause of secondary hypertension in the elderly. Unexplained hypokalemia should prompt suspicion for hyperaldosteronemia.

A urinalysis should be performed to rule out proteinuria, a sign of renovascular disease resulting from long-standing hypertension. An electrocardiogram can reveal evidence of prior myocardial infarction, arrhythmias, or left ventricular hypertrophy.

Echocardiography is the "gold standard" for diagnosis of left ventricular hypertrophy, but it is not cost-effective for every patient with hypertension. If the patient has signs or symptoms of congestive heart failure, echocardiography is indicated to measure left ventricular systolic and diastolic function. It is also indicated if the physical examination suggests the presence of valvular heart disease.

DIAGNOSING ISH

Care must be taken not to diagnose ISH on the basis of only one blood pressure reading. ISH should be diagnosed only after taking multiple readings to find average blood pressure. To find average blood pressure, blood pressure needs to be taken two or more times, and each reading must be from a different day.

As noted, the diagnosis of ISH is made by demonstrating a SBP >140 mmHg with a DBP < 90, following current recommendations for blood pressure monitoring.

The diagnosis of ISH is considered only after exclusion of other causes of widened pulse pressure such as arterio-venous fistulae, thyroid disease, anemia, aortic regurgitation, and intrinsic diseases of the artery such as coarctation.

TREATMENT OF ISH

JNC 7 issues no specific guidelines for the treatment of ISH and recommends that the management of ISH should follow the same principles outlined for general care of hypertension[21].

CLASSIFICATION AND MANAGEMENT OF HYPERTENSION: AS SUGGESTED BY JNC 7 (See Table 1)

JNC 7 recommends that all patients with Systolic blood pressure >140 mmHg, irrespective of there diastolic blood pressure, should be treated with a combination of lifestyle modification and pharmacologic therapy.

Lifestyle Modifications

Adoption of healthy lifestyles is an indispensable part of the management of those with ISH. Major lifestyle modifications shown to lower BP include weight reduction in those individuals who are overweight or obese, adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan which is rich in potassium and calcium, dietary sodium reduction, physical activity, and moderation of alcohol consumption. Lifestyle modifications reduce BP, enhance antihypertensive drug efficacy, and decrease cardiovascular risk.[21]

LIFESTYLE MODIFICATIONS TO MANAGE HYPERTENSION (See Table 2)

Pharmacologic Therapy

These are summarized in Table 2 and are useful and crucial for better managing patients with hypertension.

JNC 7 recommends that patients who have a systolic blood pressure in the range of 140-159 mmHg (Stage 1 Hypertension) should initially be treated with single antihypertensive drug and those with systolic blood pressure 160 mmHg and above (Stage 2 Hypertension) should be treated with combination drug therapy[21].

Ideal agents would target those patho-physiologic derangements that are thought to be present in ISH, and without causing serious side effects. In particular, the emergence of widened pulse pressure as a significant independent risk factor for mortality highlights the importance of avoiding agents whose actions might increase the pulse pressure—for example, agents that cause profound decreases in diastolic blood pressure. For ISH, then, a theoretic advantage would be seen in agents having a direct vasodilatory effect on the aorta and large vessels, improving arterial compliance and reversing the changes that are seen with aging and ISH.

Diuretics

Diuretics remain first-line agents in the treatment of ISH in the elderly since the impressive results of the

Table 1: Classification and management of hypertension: as suggested by JNC 7

BP classification	*SBP mmHg*	*DBP mmHg*	*Lifestyle modification*	*Initial drug therapy*	
				Without compelling indication	*With compelling indications*
Normal	< 120	and < 80	Encourage	No antihypertensive, drug indicated	Drug(s) for compelling indications
Pre-hypertension	120-139	Or 80-89	Yes		
Stage 1 Hypertension	140-159	Or 90-99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination	Drugs(s) for the compelling indications. Other antihypertensive drugs (diuretics, ACEI, ARB,BB, CCB) as needed
Stage 2 Hypertension	≥ 160	or ≥ 100	Yes	Two drug combination for most (usually thiazide-type diuretic and ACEI or ARB or BB or CCB)	

Table 2: Lifestyle modifications to manage hypertension

Modification	*Recommendation*	*Approximate SBP Reduction (Range)*
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2)	5-20 mmHg/10 kg weight loss
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low fat dairy products with a reduced content of saturated and total fat	8-14 mmHg
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride)	2-8 mmHg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week)	4-9 mmHg
Moderate of alcohol consumption	Limit consumption to no more than 2 drinks (1 oz or 30 mL ethanol; e.g. 24 oz beer, 10 oz wine,or 3 oz 80-proof whiskey)per day in most men and to nomore than 1 drink per day in women and lighter weight persons	2-4 mmHg

SHEP trial[16] with good control often seen at relatively low doses of agent. JNC 7 recommends that Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone (Stage 1 Hypertension) or in combination (Stage 2 Hypertension) with one of the other classes (ACEIs, ARBs, BBs, CCBs) demonstrated to be beneficial in randomized controlled outcome trials[21]. If a drug is not tolerated or is contraindicated, then one of the other classes proven to reduce cardiovascular events should be used instead.

Calcium Channel Blockers

Calcium channel blockers are thought to improve arterial compliance, thus reversing the mechanisms seen in ISH. In addition, they are relatively well tolerated in a number of co-morbid conditions. Both the Syst-EUR[17,18] and the Syst-China[22] studies utilized low-dose, slow-release calcium channel blockers in the treatment of ISH, with significant reductions in key end points[17,18].

Betablockers

Betablockers have proven cardio-protective effects, which make their use appealing especially in patients with known tachycardia, coronary disease, or previous myocardial infarction. Although studies have shown that propranolol may be less effective in older patients with ISH in whom reduced distensibility of the aorta is thought to be a causative mechanism[23], betablockers with intrinsic sympathomimetic activity or combined alpha-betablockers may be more effective in this population.

Nitrates

Nitrates have vasodilatory action on conduit vessels and may alter the timing of reflected pressure waves within the arterial system in a manner advantageous to treatment of ISH. The oral forms have been shown to reduce SBP without serious changes in DBP, and have been tolerated in elderly patients.

Angiotensin-converting Enzyme Inhibitors/ Angiotensin Receptor Blockers

Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce proteinuria and to slow renal disease, improve systolic dysfunction, and lower SBP in patients with ISH. It is likely that angiotensin receptor blockers (ARBs) will show similar efficacy, although they remain less studied. That ACE inhibitors have shown multiple beneficial effects in patients with coronary heart disease and nephropathy make them an especially attractive therapy for patients with ISH and these co-morbid conditions. Several recent studies have also confirmed the benefit of ARBs for the nephropathy of type 2 diabetes mellitus.

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