Isolated systolic hypertension : A robust risk factor for cardiovascular diseases

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Abstract
Isolated systolic hypertension has become largely a disease of older people; since the rapidly aging of the world population, inadequate control of systolic blood pressure rather than diastolic hypertension is by far the pressing public health problem. Different prospective cohort studies have shown that BP is positively, continuously and independently associated with increased risk of cardiovascular and renal diseases. Several epidemiological studies have shown that systolic and diastolic curves relating blood pressure to the risk of CV events are parallel and that systolic blood pressure is at least as important as or even more than diastolic blood pressure as a risk factor for CV complications. The Multiple Risk Factor Intervention Trial (MRFIT) has shown that the risk of coronary artery disease was more strongly related to SBP (3.7 times from the lowest to the highest deciles) than to DBP (2.8 times). In the adult Framingham Heart Study, SBP appears to play a more important role than DBP for all the clinical manifestations of CHD (acute myocardial infarction, angina and sudden death). Many observational studies have demonstrated that SBP is a stronger predictor of the risk of stroke than DBP.

Introduction
Hypertension remains the major risk factor for cardiovascular diseases (CVD) i.e strokes, coronary artery disease and heart failure. But until the 1980's diastolic blood pressure (DBP) was the most relevant haemodynamic parameter as a predictor of prognosis in hypertensive patients. Accordingly, most clinical studies particularly addressed DBP and DBP values were put forward as goals for treatment. Since then a radical change in thinking, based upon epidemiological studies has led to the recognition of elevated systolic blood pressure (SBP) as a risk at least as important as high DBP. Certain studies would even indicate that SBP is a more relevant predictor of prognosis than DBP, in particular with the risk of stroke. For this and other reasons, the term Isolated Systolic Hypertension (ISH) has been introduced for those subjects with elevated SBP and normal (or even lower) DBP. This condition is found particularly in elderly hypertensive, since SBP is known to rise with advancing age, whereas DBP usually levels off and then tends to decrease in the elderly. Consequently, pulse pressure (SBP minus DBP) will increase in such patients. It appears that elevated pulse pressure is an even better predictor of cerebral and cardio-vascular events in elderly hypertensives than a high SBP as such. Indeed, ISH is the most common type of hypertension in the elderly and it is the most prevalent type of untreated hypertension among persons over 60 years of age. According to the modern definitions, expressed in the JNC-VI and 1999 WHO/ISH-Guidelines. ISH is now defined as BP >140/<90mmHg. These criteria are most 'stringent' than the older definition of ISH at >160/<90 mm Hg.

Pathophysiology of ISH
The basic mechanism for progressive rise in systolic blood pressure (SBP) with age is loss of distensibility and elasticity in large capacitance vessels from atherosclerosis. The proliferation of connective tissue in the walls of large vessels results in intimal thickening and fibrosis. This leads to loss of arterial compliance and the large vessels become less...
able to reduce the pressure generated by the left ventricle by means of distension. Consequently the pulse pressure and pulse wave velocity increase causing a disproportionate increase in SBP. On the other hand, with the increased arterial stiffness and reduce caliber of large capacitance vessels, the normal drain off into peripheral vasculature during diastole leaves less blood filling these vessels, thus reducing the diastolic blood pressure (DBP). These counteracting forces may keep the diastolic pressure normal in the setting of an increasing systolic pressure.

**Prevalence of ISH**
Recent estimates from the American National Health and Nutrition and Examination Survey (NHANES III) have shown the following:
- ISH is the most common form of hypertension in the elderly and tends to worsen with advancing age.
- ISH accounts for 54% of hypertension in patients aged 50-59 years and 87% in patients aged 60 years or older.
- ISH patients comprise the largest group of uncontrolled hypertensive patients.
- 65% of uncontrolled hypertensive patients have ISH.
- Systolic hypertension is more common in women than men and in the black population.

**Isolated systolic hypertension as a risk factor**
The presence of hypertension poses an additional risk for cardiovascular damages at all ages. The widened pulse pressure found so typically in the elderly reflects both an increase in systolic and a decrease in diastolic pressure. Several studies, including the Framingham study, documented the risk of high SBP in particular with respect to stroke and less clearly, ischemic heart disease. Similarly, in the MRFIT study SBP was found to be a stronger predictor of outcome than DBP. However, it should be realized that too low a DBP is also dangerous. Compared with normotensive patients, those with ISH have more coronary artery disease and even more stroke with an approximate 1% increase in all cause mortality rates with each 1 mm Hg rise in systolic pressure. These observations once more emphasize the important role of widened pulse pressure as a risk factor. Consequently, several intervention studies in patients with ISH have demonstrated the beneficial effect of the treatment of ISH and more generally of treatment of hypertension in the elderly. At least on theoretical grounds it seems desirable to lower SBP in such patients without simultaneously lowering DBP in order to avoid a further widening of pulse pressure.

**Treatment of ISH**
The therapeutic approach should include modification of inappropriate lifestyle habits and for most patients appropriate antihypertensive therapy. In general terms, the beneficial effect of treatment of ISH runs in parallel with that of the treatment of hypertension in the elderly. Treatment of hypertension in elderly patients differs in a number of both obvious and subtle ways from the treatment of younger patients. In part, this is a reflection of the different pathophysiology described earlier, although mainly it is because of the multiple natural changes occurring with age. Elderly patients need to be treated cautiously, following the admonition: start low and go slow.

Since the elderly may have sluggish baroreceptor and sympathetic nervous responsiveness, as well as impaired cerebral auto-regulation, therapy should be gentle and gradual, avoiding drugs that are likely to cause postural hypotension or to exacerbate other common problems often seen among the elderly like--cerebral ischemia, hyponatraemia, arrhythmia, muscular weakness, drug accumulation, depression, confusion etc. These cautions should not, however, interfere with the well-documented need to treat the overwhelming majority of elderly patients with hypertension. The benefits that elderly people have been shown to receive from antihypertensive drug therapy are quantitatively greater than those provided to younger patients. No longer should age alone interfere with the provision of appropriate therapy.
In general, this issue has been addressed since the 1990s by means of intervention trials. Several trials such as STOP-1, STOP-2 and MRC elderly have clearly shown that treatment of hypertension in the elderly protects against the complications of hypertension, particularly stroke. A few other clinical trials have deliberately addressed a population of patients with ISH as such- Systolic Hypertension in the Elderly Program (SHEP), Systolic Hypertension in Europe (SYST-EUR), SYST-China trial and INSIGHT study etc. The deterioration of arterial compliance especially of the large conduit arteries results in elevated systolic pressure which places additional metabolic demands on an already stressed myocardium whereas; the decrease in diastolic pressure reduces coronary artery perfusion. Drugs such as long-acting dihydropyridine calcium channel blockers (CCBs) are beneficial in the treatment of ISH in the elderly because apart from their antihypertensive efficacy, they improve endothelial function and may positively influence atherosclerosis, improving arterial compliance. Moreover, they confer the additional benefit of reducing the risk of developing vascular dementia. The combination of natural ageing and hypertensive nephrosclerosis reduces the amount of renin secreted from kidney. Therefore, elderly patients with hypertension have low plasma renin activity and tendency to retain sodium.

These patients are more sodium sensitive and have a greater fall in blood pressure when put on reduced sodium diet or given a diuretic. A combination of dihydropyridine calcium channel blocker and a thiazide type diuretic improves arterial compliance, the root cause of ISH and offers significant reduction in difficult-to-treat systolic hypertension. At least on theoretical grounds it would seem desirable to find antihypertensive drugs which reduce SBP more markedly than DBP. Newer drugs such as ACE-inhibitors, AT1-blockers and omapatrilate are effective in lowering SBP in ISH patients, but large-scale data concerning their protective effects are not available.

Conclusions
Isolated systolic hypertension is characterized by a widened pulse pressure. It has been recognized as an important entity, which requires consistent treatment. Appropriate management of patients with ISH can be difficult and expensive in both time and money, but the rewards are well worth the effort. Lifespan may be lengthened by some amount, however, the major benefits derive from the prevention of disabling events-stroke, heart failure, coronary and peripheral vascular diseases- the common comorbidities associated with elevation of systolic blood pressure. Apart from well-known advices for lifestyle modification, drug treatment is required in the majority of patients with ISH. The data so far available indicate that low dose thiazide diuretics and long acting calcium antagonists are the drug of choice. A slow reduction of systolic pressure in the mostly elderly patients is mandatory. A target level of SBP around 140 mm Hg seems desirable.

References
6. The sixth report of the Joint National Committee on detection, evaluation, and