AGEING SERIES

Blood pressure and ageing

Elisabete Pinto

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Isolated systolic hypertension, an elevation in systolic but not diastolic pressure, is the most prevalent type of hypertension in those aged 50 or over, occurring either de novo or as a development after a long period of systolic-diastolic hypertension with or without treatment. The increase in blood pressure with age is mostly associated with structural changes in the arteries and especially with large artery stiffness. It is known from various studies that rising blood pressure is associated with increased cardiovascular risk. In the elderly, the most powerful predictor of risk is increased pulse pressure due to decreased diastolic and increased systolic blood pressure. All evidence indicates that treating the elderly hypertensive patient will reduce the risk of cardiovascular events. However, there is no evidence yet for the very elderly. This population is particularly susceptible to side effects of treatments and the reduction of blood pressure, although reducing the risk of cardiovascular events such as stroke, may result in increased mortality.

An increase in blood pressure (BP) has always been taken as an inevitable consequence of ageing in industrialised societies, leading to hypertension in a high proportion of elderly subjects. However, the characterisation and definition of what constitutes hypertension in the elderly has changed over the years. Data obtained during the Framingham Heart Study, which followed patients for 30 years, agreed that systolic blood pressure (SBP) shows a continuous increase between the ages of 30 and 84 years or over. Diastolic blood pressure (DBP), however, has a varying pattern with ageing, increasing until the fifth decade and slowly decreasing from the age of 60 to at least 84 years of age. This leads to a steep rise in pulse pressure (PP) with ageing.[1] Isolated systolic hypertension (ISH) (or simply systolic hypertension as some authors prefer, as the term isolated systolic hypertension may minimise the perceived health risk[2]) is consequently most prevalent in those aged 50 or over. The third National Health and Nutrition Examination Survey (NHANES III) in the US showed that almost 80% of those individuals aged 50 or over with high BP, at least on a single occasion, have systolic hypertension.[3] This and other studies also showed that this type of hypertension was the least well managed, perhaps because it particularly affects the elderly.[4] Hypertension in older subjects may be defined as SBP≥140 mm Hg or SBP≥160 mmHg and/or a DBP≥90 mm Hg. Systolic hypertension is either observed de novo or as a development after a long period of systolic-diastolic hypertension with or without treatment.

The Framingham Heart Study also showed that cardiovascular risk is positively, continuously and independently associated with rising BP.[1] High DBP has been employed as the main determinant of hypertension-associated cardiovascular risk as studies have shown it to be an independent risk factor[5] and earlier intervention trials have focused on the benefits of lowering DBP to reduce risk. But in older individuals, high SBP and high PP have been shown to be more powerful independent predictors of risk, specially increased PP due to decreased DBP and elevated SBP.[1] The MRFIT trial showed that although raised DBP and SBP predicted increased death from coronary heart disease (CHD), the risk was greater with each increment of SBP and that individuals with ISH were at the greatest risk of death from CHD.[6] The risk of stroke was also strongly related to SBP and ISH.[7] The danger of cardiovascular complications associated with a widening PP was also shown in a meta-analysis that included results from several major trials including SHEP, EWPHE, Syst-Eur and Syst-China (table 1).[8]

The Prospective Studies Collaboration[24] obtained information from almost 1 million adults with no previous cardiovascular disease at baseline, who participated in 61 prospective observational studies of BP and mortality. BP was found to be associated strongly with the age-specific mortality rates for stroke, ischaemic heart disease and other vascular diseases. The relationship between stroke mortality and BP was present from 40 up to 89 years of age for BP increasing from as low as 115 mm Hg for SBP and 75 mm Hg for DBP. However, the strength of the association between the relative risk of fatal stroke and usual BP decreases with increasing age at death. Similar results were found for mortality due to ischaemic heart disease.

In the UK, stroke and CHD are the major causes of death in people over 65 years of age. The most common treatable risk factor is hypertension.[25] Hypertension treatment can prevent stroke and its recurrence, significantly reducing risk.[26 27] Several studies in the elderly have shown that antihypertensive medication reduces the incident of stroke.[28]

Some studies in elderly patients with hypertension have shown a J-curve relationship between

Correspondence to:
E Pinto, Faculty of Medicine, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK; e.pinto@imperial.ac.uk

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Abbreviations: BP, blood pressure; CHD, coronary heart disease; DBP, diastolic blood pressure; ISH, isolated systolic hypertension; LAS, large artery stiffness; NHANES III, the third National Health and Nutrition Examination Survey; OH, orthostatic hypotension; PP, pulse pressure; PPH, postprandial hypotension; PVR, peripheral vascular resistance; SBP, systolic blood pressure

Table 1 Summary of clinical trials demonstrating the value of lowering blood pressure in hypertensive subjects aged 60–79 years

Trial	Entry criteria	n	Age	Treatment	Results/update
ANBP 2	SBP≥160 mm Hg DBP≥90 mm Hg	6083	65–84 years	ACE inhibitor or diuretic based regimen	Similar reduction in BP in both groups. ACE inhibitor reduced cardiovascular events or death (p=0.05)
EWPHE	SBP 160–239 mm Hg DBP 90–119 mm Hg	840	≥60 years (mean 72 years)	Hydrochlorothiazide and triamterene with possible addition of methyldopa or matching placebo	No significant reduction in total mortality. Significant reduction in cardiovascular mortality (p<0.05) and non-fatal cerebrovascular events (p<0.05)
MRC	SBP 160–209 mm Hg DBP<115 mm Hg	4396	65–74 years	Diuretic, β-blocker or placebo	Diuretic reduced stroke (p=0.04), coronary events (p=0.001) and cardiovascular events (p=0.001) compared with placebo
SCOPE	SBP 160–179 mm Hg and/or DBP 90–99 mm Hg, Mini Mental State Examination≥24	4964	70–89 years	Candesartan, cilexetil or placebo	Candesartan reduced non-fatal stroke (p=0.04) and all stroke events (p=0.056). Cognitive decline and development of dementia was similar in both groups
SHELL	SBP≥160 mm Hg DBP≤95 mm Hg	1882	≥60 years	Lacidipine or chlorthalidone	Both treatments reduced SBP and DBP (p<0.001). Total mortality and cardiovascular events were similar in both groups
SHEP	SBP 160–219 mm Hg DBP<90 mm Hg	4736	≥60 years (mean 72 years)	Chlorthalidone titrated or changed to atenolol or placebo	Stroke was reduced (p=0.001) and major cardiovascular events were reduced in the active treatment group
STOP-Hypertension 2	SBP≥180 mm Hg and/or DBP≥105 mm Hg	6614	70–84 years	β-Blockers and/or diuretics compared with ACE-inhibitors or calcium antagonists	No difference was found in the prevention of cardiovascular mortality or major events between the groups
Syst-Eur	DBP<95 mm Hg SBP 160–219 mm Hg	4695	≥60 years (mean 70 years)	Nitrendipine plus enalapril and/or hydrochlorothiazide as necessary and matching placebos	Active treatment reduced all strokes (p=0.003) and non-fatal strokes (p=0.007). Fatal and non-fatal cardiac endpoints also decreased (p=0.03)
Syst-China	SBP 160–219 mm Hg DBP<95 mm Hg	2394	≥60 years (mean 66.5 years)	Nitrendipine plus captopril, and/or hydrochlorothiazide if necessary and matching placebos	Active treatment reduced stroke (p=0.01), stroke mortality (p=0.02), all-cause mortality (p=0.003), cardiovascular mortality (p=0.03) and all fatal and non-fatal cardiovascular endpoints (p=0.004)

ANBP 2, Second Australian National Blood Pressure Study Group[9 10]; EWPHE, European Working Party on High Blood Pressure in the Elderly[11]; MRC, Medical Research Council trial of treatment of hypertension in older adults[12]; SCOPE, Study on Cognition and Prognosis in the Elderly[13 14]; SHELL, Systolic Hypertension in the Elderly Long-term Lacidipine trial[15 16]; SHEP, Systolic Hypertension in the Elderly Program[17]; STOP-Hypertension 2, Swedish Trial in Old Patients with Hypertension[18 19]; Syst-Eur, Systolic Hypertension in Europe[20 21]; Syst-China, Systolic Hypertension in China.[22 23]

BP and stroke events in those treated for hypertension. A sub-analysis of the SHEP trial showed that a decrease in DBP increased the risk of stroke in the treated group.[29] A prospective cohort study of a elderly Dutch population showed a J-curve relationship between BP, particularly DBP, and stroke risk.[30]

Hypertension is more common in people with diabetes, particularly ISH. In diabetes type II, hypertension is more common in women than in men and the age-related increase in SBP is steeper in women.[31] Trials have shown that lowering BP reduces major cardiovascular events in those with diabetes.[32 33] For cardiovascular and also renal protection, people with diabetes require good BP control and so most patients with diabetes and hypertension require combination therapy to achieve targets.[34 35]

Increase in BP was thought to be an unavoidable consequence of ageing. It is known, however, that in secluded communities and in rural and underdeveloped areas this is not the case. Also, studies of populations who migrated from underdeveloped to developed areas show a change towards an increase in BP, possibly due to change in diet, reduction in exercise and increase in stress.[36] In certain communities a correlation was found between salt excretion, levels of sodium in the diet and SBP and PP.[37 38] These and other observations suggested that a high salt diet may induce changes in the vascular smooth muscle cells resulting in collagen accumulation in the large artery walls and consequent increased arterial stiffness.[39] The increase in BP with age is most likely due to complex and varied factors moulded and influenced by the individual environment and lifestyle.

In some individuals BP decreases with ageing. This is mostly as a consequence of illness such as Alzheimer's and other forms of dementia, cancer or impaired ventricular function which may occur after myocardial infarction. Starr and co-workers followed a cohort of around 600 elderly people aged 70 and over in the HOPE (Healthy Old People in Edinburgh) study. After a follow up of 4 years, they observed that retired unskilled workers had a reduced ageing-related increase in BP. They determined that this lower BP was due to underlying disease. They found that SBP continues to increase in subjects free from disease, although DBP had an initial rise but then fell back to baseline levels.[40] It is not only disease per se that can alter the increase in BP with ageing. The use of medication can also change the relationship between disease and BP. The length of disease duration and the increased requirement of regular drug treatment also affect the increase in BP with age. Some studies, such as the Leiden study, showed an inverse relationship between increased BP in the elderly and mortality. This may be due to poor health. Alternatively, those who live longer despite high BP may be a selected group.[41] A similar inverse association between BP and mortality was also found in the Helsinki Ageing study, a population-based study of over 500 people aged 75 or over. This association remained after adjustment for disease, although the authors indicated that comorbidity could not be totally excluded. However, the study suggested that antihypertensive treatment in those aged 80 years or over could be problematic due to falling BP and increased mortality.[42]

PATHOPHYSIOLOGY

Increase in BP with age is mostly related to changes in arterial and arteriolar stiffness. Large artery stiffness (LAS) is mainly due to arteriosclerotic structural alterations and calcification. This leads to earlier reflected pressure waves from the arterioles towards the heart during BP wave propagation. These pressure waves arrive back during systole increasing central SBP and widening PP.

The increase in DBP up to the age of 50 is mostly due to increased peripheral vascular resistance (PVR) in small vessels. However, both LAS and PVR contribute toward the increase in SBP, while DBP increases with PVR but decreases with the

increase in LAS. Although PVR may initiate hypertension, it is the acceleration of LAS that leads to the steeper rise in SBP after 50 years of age.[43]

The structural changes in large arteries observed in systolic hypertension are very similar to those resulting from the ageing process. This makes it difficult to differentiate between the arterial changes due to disease and those due to ageing.[39]

Other pathophysiological influencing factors which contribute to the increase in BP with ageing include decreased baroreceptor sensitivity, increased responsiveness to sympathetic nervous system stimuli, altered renal and sodium metabolism and an altered renin-aldosterone relationship.[44]

EPIDEMIOLOGY

The criteria used to define hypertension have changed in the last few decades. A study of the management and control of hypertension in England in those over 64 years of age included 3500 subjects and showed that 81% had ''hypertension'' at a single time point, according to the 1999 definition of the British Hypertension Society (SBP≥140 mm Hg or DBP≥90 mm Hg). This study showed that 78% of men and 83% of women were ''hypertensive''. In the untreated hypertensive subjects, 76% had ISH (71% of men and 82% of women; SBP≥140 mm Hg and DBP<90 mm Hg). The same study found that in treated hypertensive patients, the mean SBP was above target whereas the average DBP values were consistently below target for all ages.[45] This could be either because clinicians still focus on DBP, although the subjects have ISH, or because SBP is more difficult to treat due to the underlying changes in large blood vessels.

The NHANES III study in the US found a similar pattern of results. ISH was found predominantly in the older population, accounting for 87% of hypertensive patients after the sixth decade of life, and was the most common type of hypertension in the untreated and inadequately treated hypertensive subjects.[3]

Considering that the association with cardiovascular events is stronger for SBP, at least for those between 40 and 80 years of age, there is need to focus attention on the control of SBP.

A few studies have showed a difference in the age-related rise in BP with gender.[46 47] The Framingham Heart Study showed a higher prevalence of ISH in elderly women than in elderly men.[48] This may be because elderly hypertensive women have stiffer large arteries, greater central wave reflection and consequently a higher PP than elderly men. It is known that younger women have less stiff arteries compared with men of similar age.[49 50] The increased arterial stiffness occurs after the menopause and could explain the rapid acceleration of cerebrovascular and cardiovascular events in elderly women. However, these rates always remain lower than in elderly men.[51] A study of over 600 subjects with a mean age of 71 found decreased systemic arterial compliance (lower functional compliance), a higher augmentation index (greater central wave reflection) and increased PP in women independent of other variables. This was true even though mean arterial pressure was slightly higher in men.[52]

An observational study of 150 Swedish subjects, aged 67 or over and followed up for 25 years, found that women had a higher average BP regardless of whether they were hypertensive or not. Whereas hypertension and high BP in men increased mortality risk, in women the cardiovascular mortality risk was similar for hypertensive and normotensive subjects.[53] This suggestion needs to be confirmed in larger studies.

SPECIAL CONDITIONS ASSOCIATED WITH ELDERLY HYPERTENSIVE SUBJECTS

Orthostatic hypotension

Orthostatic hypotension (OH) is known to affect the elderly more than younger subjects and could lead to an increase in falls and dangerous fractures in this population. The usual definition of OH is a fall in SBP of at least 20 mm Hg or a DBP fall of at least 10 mm Hg within 3 min of standing. In a survey, Rutan and co-workers[54] found the prevalence of OH to be 17% in those 65–74 years of age and 26% in those aged over 85. In the Hypertension in the Very Elderly (HYVET) pilot study, involving patients aged 80 years or over, 7.7% of patients showed systolic OH and 5.4% of patients showed diastolic OH. In total, it was estimated that 12% of this population had OH. The fall in SBP tended to be greater for women over the age of 90, although this excess was not statistically significant.[55]

OH is a cause of morbidity and mortality due to falls and syncope, but it may also be a cardiovascular risk factor. Kario and co-workers[56] found an increase in silent cerebrovascular disease in elderly patients with OH.

The postural fall in BP seen in the elderly could be due to a decrease in baroreflex sensitivity and a deficient heart-rate response to the change in posture.[57] James and Potter found a relationship between baroreflex sensitivity and SBP fall during orthostasis even after adjusting for SBP. The drop in SBP was also higher in hypertensive than in normotensive subjects.[58]

Drug-induced orthostatic reactions occur at a frequency of 5%–33% in geriatric patients and can lead to syncope and falls; 11% of the cases of syncope in the elderly are reported to be drug-induced.[59]

Postprandial hypotension

Postprandial hypotension (PPH), that is a reduction in BP after meals, has been recognised as a common cause of syncope and falls in healthy and hypertensive elderly individuals. The ambulatory blood pressure monitoring side project of the Syst-Eur trial which included 530 patients with a mean age of 70 years, showed that both SBP and DBP decreased after food reaching a minimum 1–2 h after a meal. About 70% of patients showed a decrease in BP and around 24% of patients showed a decrease in SBP of more than 16 mm Hg and a decrease in DBP of more than 12 mm Hg. As shown in other studies the heart rate remained unchanged.[60]

Puisieux and colleagues studied patients hospitalised due to syncope or fall with a mean age of 80 years and found a decrease in SBP after all meals, especially breakfast. The change in SBP was significantly higher in the patients with syncope. PPH was higher in the syncope/fall group (23%) compared with controls. They also found that PPH was more common in patients with higher daytime SBP variability.[61]

A possible reason for PPH could be the increased concentration of vasoactive gastrointestinal peptides or insulin-related vasodilation.[62]

BP variability

Pringle and co-workers[63] analysed SBP variability, as part of the Syst-Eur trial, and found it to be positively correlated to increasing age. After adjustment for SBP, BP variability, especially night-time variability, was a predictor of stroke. The risk of stroke increased by 80% for each 5 mm Hg increment in night-time SBP variability.[63]

Longitudinal studies, such as the Ohasama study in rural Japan which followed over 1500 participants for 8.5 years, showed an increase in circulatory system-associated mortality with the highest quintile of BP variability at night (>14.4 mm Hg). However the same was not true for total mortality.[64]

Other studies have associated a morning surge in BP[65] and changes in the nocturnal dipping of BP with increased risk of stroke.[66–68]

White coat hypertension

White coat hypertension, also termed non-sustained hypertension, is a common phenomenon in the elderly. In the Syst-Eur

trial, 24% of patients had a 24 h mean SBP lower than 140 mm Hg when the entry criteria was 160–219 mm Hg.[69] BP variability may also be related to white coat hypertension. A study comparing 33 centenarians (25 men and 8 women) with 100 subjects aged 65–70 years found that ambulatory blood pressure monitoring measurements were lower than the clinic pressure with higher white coat effect and higher BP variability in the centenarians.[70]

Regarding the risk of cardiovascular events with white coat hypertension, studies have shown contradictory results,[2] although a 10 year follow-up study indicated that white coat hypertension is associated with increase risk of cardiovascular events.[71] Another study has suggested no benefit of treating patients with white coat hypertension, although the risk was higher than in normotensive subjects.[72]

In the Syst-Eur trial, patients with sustained hypertension had higher cardiovascular complications than those with white coat hypertension, and there were no statistically significant benefits of anti-hypertensive treatment in patients with white coat hypertension.[69]

MANAGEMENT OF BLOOD PRESSURE IN THE ELDERLY

The very elderly

The trial data indicate that treating elderly hypertensive patients will reduce the risk of cardiovascular events. However, there is no evidence to date regarding treatment of the very elderly, namely those over 80 years of age. A meta-analysis of clinical trials of antihypertensive treatment concluded that although treatment in those aged 80 or over can reduce the risk of stroke, it does however increase total mortality.[73] The results from the HYVET pilot trial[74] agreed with this (the main HYVET trial is ongoing[75]).

There is evidence that many physicians are unsure about treating very elderly patients. A survey of physicians in the US showed that 35% of physicians believed that the BP increase was a normal part of the ageing process, whereas 25% considered that treating the very elderly (>85 years) with mild to moderate hypertension could have more risks than benefits.[76]

Special considerations

The first drug of choice for elderly patients still seems to be a thiazide or in some cases a calcium channel blocker.[2] The SHELL trial (table 1) compared these two classes of drugs and found no difference in cardiovascular events or mortality with the same BP reduction.[16] Diuretics may be better at preventing cardiovascular events when compared with β-blockers, as suggested by a meta-analysis.[77]

It is beyond the scope of this article to elaborate on the most appropriate drug therapy or on the details of any particular class of antihypertensive drugs. However, there are a few considerations regarding treatment.

A possible problem, especially when treating ISH, is the widening PP. The Syst-Eur trial showed that higher PP at enrolment was correlated with poorer cardiovascular prognosis.[78] Analysis of the SHEP data (table 1) showed an increased risk of cardiovascular events with an increased PP and a dose–response effect to lowering DBP.[79]

There is an increase in the side effects of medication due to the altered pharmacokinetics and pharmacodynamics in the elderly. Low body weight and frailty in the very elderly may mean that these patients receive higher doses of medication per unit body weight than other less frail patients, contributing to the risk of overmedication. The nutritional status of the elderly also affects the rate of drug metabolism and in the frail elderly drug metabolism is reduced.[59] ACE inhibitors, often used as second line agents, can cause persistent dry cough in as many as 10–20% of patients due to inhibition of bradykinin breakdown. This leads to discontinuation and poor compliance.[80] Long-term therapy with diuretics and the decrease in body water and reduction of fluid intake in the elderly could lead to an increased risk of hypokalaemia and hyponatraemia, especially in females, when compared with younger patients.[59]

It is preferable to use a once daily dose to increase compliance and start each drug at a low dose to avoid reducing the BP too much or increasing the chance of side effects. Co-morbidities need to be taken in consideration in the use of medication both in terms of advantages such as the use of β-blockers in angina or contra-indications such as β-blockers in peripheral vascular disease.[80]

The elderly patient should be aware of all benefits and risks and shared decision-making is probably the most appropriate option. This involvement of the patient could improve adherence to the treatment and consequent outcome. However, there is a lack of literature on how to do this in very elderly patients.

Lifestyle changes

Because the treatment of those with hypertension may not be acceptable and may even be detrimental in the very elderly, life-style changes starting in middle age or perhaps earlier could slow or delay progression of the condition and could reduce the burden of related cardiovascular events. However, such life-style changes may be more difficult in the elderly, who may be more adverse to salt restriction or would find an exercise program difficult to follow.

There are few conclusive trials in the elderly hypertensive patient regarding life-style modification. The TONE trial (Trial of Nonpharmacological Intervention in the Elderly) showed a reduction in cardiovascular complications and requirement for drugs after a reduction in salt intake.[81] Salt reduction may also have other health related benefits independent of the BP effect, such as a reduction in target organ damage.[82] Salt reduction is possibly effective in the elderly because of decreased arterial compliance and hence a decrease in arterial blood volume which leads to a larger drop in BP.[83]

Intervention exercise programs were also implemented in elderly hypertensive patients such as that conducted by Motoyama and co-workers. However, although these programs were effective at reducing SBP and DBP within a few weeks, once the study was stopped the amount of exercise declined and BP returned to baseline levels.[84]

CONCLUSION

The criteria used to define hypertension have changed with time, but although the cut-off points are not agreed by all physicians, it is certain that the elderly have predominantly isolated systolic hypertension and that its treatment can reduce the risk of cardiovascular events. The treated elderly have increased such as orthostatic and postprandial hypotension and increased BP variability. These problems and the increased burden of side effects and comorbidities with ageing, need to be taken into consideration when treating elderly and particularly very elderly hypertensive patients, in whom the balance of risk and benefit from anti-hypertensive treatment remains to be determined.

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