Isolated Systolic Hypertension and the Risk of Vascular Disease

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Hypertension is present in 60% to 70% of the population over 60 years of age and may result in cardiovascular complications such as stroke, coronary heart disease, and heart failure. In this review, the role of arterial stiffness, endothelial function, atherosclerosis, and oxidative stress in the pathogenesis of hypertension is discussed extensively. Antihypertensive drug treatment may control high blood pressure and prevent complications. This review summarizes the results of several placebo-controlled and comparative clinical trials that have studied the efficacy of different classes of antihypertensive drugs.

Introduction

Essential hypertension refers to a lasting elevation of blood pressure with heterogeneous genetic and environmental causation. Its prevalence rises with age regardless of the type of blood pressure measurement and is dependent on the operational thresholds used for diagnosis. Aging is also associated with a steep increase in vascular diseases. This article reviews the risk between vascular diseases and isolated systolic hypertension from a clinical, epidemiologic, and pathophysiologic perspective.

Epidemiology

In cross-sectional and longitudinal population studies, systolic blood pressure (SBP) increases with age, while diastolic blood pressure (DBP) rises until 50 years of age and then levels off or even slightly decreases [1]. Consequently, with increasing age there is a shift from diastolic pressure to systolic pressure and then to pulse pressure as the predominant predictor of cardiovascular risk. In the Framingham Heart Study, DBP was the strongest predictor below age 50 years, all three blood pressure indexes were

comparable predictors at ages 50 to 59, and from 60 years on, DBP was negatively related to risk of coronary events, so that pulse pressure became superior to SBP [2••]. The predictive role of pulse pressure in the elderly is consistent in men and women, in treated and untreated hypertensive subjects [3•], and in patients with a history of myocardial infarction [4] or renal failure [5]. Furthermore, in older patients with isolated systolic hypertension, pulse pressure [6], and especially ambulatory pulse pressure [7], is a stronger predictor of cardiovascular risk than mean pressure.

According to guidelines proposed by the European Society of Hypertension (ESH)/European Society of Cardiology ESH/ESC [8], hypertension is defined as SBP of 140 mm Hg or higher, DBP of 90 mm Hg or higher, or taking antihypertensive drug treatment (Table 1). The prevalence of hypertension is about 25% in the general adult population and increases to 60% to 70% in the age group above 60 years [1]. In the general US population studied in the National Health and Nutrition Examination Survey III (NHANES III), men had a higher prevalence of hypertension than women up to 59 years, while the reverse was true from 60 years on [1].

Isolated systolic hypertension, defined as SBP of 140 mm Hg or higher and DBP below 90 mm Hg (Table 1), is the predominant type of hypertension in the elderly. The NHANES III data demonstrated that below the age of 50 years, isolated diastolic hypertension (SBP below 140 and DBP 90 mm Hg or more) was most common (46.9%) among untreated hypertensives, while combined systolic/diastolic hypertension (SBP 140 mm Hg or more and DBP 90 mm Hg or more) was most common (45.1%) among inadequately treated individuals. In both untreated and inadequately treated groups, isolated systolic hypertension became the primary hypertensive subtype for subjects after the age of 50 years.

Few studies provide information on the incidence of hypertension in the general population. In the Framingham Heart Study, 5.3% of participants with optimal blood pressure, 17.6% with normal, and 37.3% with high-normal blood pressure below the age of 65 years developed hypertension over a period of 4 years [9•].

Pathophysiology

Pulse pressure, the difference between SBP and DBP, is determined by the compliance of the arterial vascular bed and the

Table 1. Definitions and classification of blood pressure levels (mm Hg) based on conventional blood pressure measurement in adults aged 18 years and older, not taking antihypertensive drugs and not acutely ill

	Systolic blood pressure, mm Hg		Diastolic blood pressure, mm Hg	
Normotension				
Optimal	< 120	and	< 80	
Normal	120–129	or	80–84	
High-normal	130–139	or	85–89	
Hypertension				
Grade 1 (mild)	140–159	or	90–99	
Subgroup borderline	140–149	or	90–94	
Grade 2 (moderate)	160–179	or	100–109	
Grade 3 (severe)	≥ 180	or	≥ 110	
Isolated systolic hypertension	≥ 140	or	< 90	
Subgroup borderline	140–149	or	< 90	

stroke volume, and to a lesser extent by the ejection rate of the left ventricle. Mean arterial pressure, a weighted average of SBP and DBP, is dependent on cardiac output and total peripheral resistance. Isolated systolic hypertension, by definition, is characterized by an increase in pulse pressure, but not necessarily by an increase in mean arterial pressure.

Arterial stiffness as a determinant of isolated systolic hypertension

Arterial stiffness is emerging as the most important determinant of primary isolated hypertension in our aging community. Arterial distensibility and pulse wave velocity reflect the elasticity of an artery. Aortic pulse wave velocity doubles while distensibility coefficients halve between 20 and 70 years of age, (Fig. 1 A and B). The arterial pressure wave consists of a forward component generated by the heart and reflected waves returning to the heart from peripheral sites [5]. In healthy young adults, the reflected waves coincide with diastole, raise diastolic pressure, and boost coronary perfusion. With arterial stiffening, the reflected waves move faster, reach the proximal aorta during systole, and cause an augmentation of late systolic pressures, whereas diastolic pressure decreases. The early return of the reflected pulse wave to the aorta during systole is the primary mechanism accounting for the rise in SBP and the decline in DBP that occurs with arterial stiffening. Lowered diastolic pressure may impair coronary blood flow and predispose to myocardial ischemia. The higher systolic pressure augments cardiac work and may lead to heart failure [5]. Histopathologic examination of the aorta of the elderly reveals thickening of the media due to the accumulation of collagenous fibers as well as calcium deposition [10]. A functional component may be superimposed on these structural changes. Indeed, the vasoconstrictor tone in the large arteries may well rise with age, when the number of β_2 -adrenoreceptors that mediate vasodilatation decreases [11].

Endothelial function and arterial stiffness

Endothelial function estimated as flow-mediated vasodilatation apparently starts to deteriorate at about 50 years of

age (Fig. 1C), *ie*, when pulse pressure begins to rise. Endothelial function is more per formant in premenopausal women than in men. This observation suggests that estrogens might enhance endothelial function. Indeed, estrogens activate endothelium-dependent vascular relaxation mechanisms, including the nitric oxide-cGMP and prostacyclin-cAMP pathways [12].

The endothelium generates a variety of biologic mediators that influence the tone and structure of the blood vessel and determine the susceptibility of the vessel wall to atherogenesis. One of these mediators is nitric oxide, which is synthesized from the amino acid L-arginine via the action of the enzyme nitric oxide synthase.

Endothelin-1 is an important vasoconstrictor released by the endothelium and may also increase arterial stiffness. Indeed, plasma endothelin-1 concentration shows a significant positive correlation with aortic stiffness in patients with coronary artery disease [13]. This observation illustrates that endothelial function affects the function of large arteries. Thus, large arteries are more than simply passive conduits.

Atherosclerosis in isolated systolic hypertension

Many of the histologic alterations that occur in the vessel wall with aging resemble those that come with atherosclerosis. Figure 1D shows the increase in carotid intima media thickness, a sign of early atherosclerosis associated with advancing age. Nevertheless, the role of atherosclerosis in the pathogenesis of isolated systolic hypertension remains debatable. In autopsy specimens of human aorta, compliance decreases with age, but the relative contributions of aging and atherosclerosis remain unknown [14]. Moreover, clinical experience shows that many patients with severe generalized atherosclerosis maintain a normal central compliance. In contrast, in some populations with a low prevalence of atherosclerosis, systolic pressure does rise with age and isolated systolic hypertension is observed [15].

Hypertension: cause or effect of arterial stiffness?

Whether the acceleration of the aging process occurs through an increase in arterial stiffness or through hyper-

Figure 1. Wall characteristics by gender and age in a sample of the general population. Squares represent men and circles represent women. **A**, Pulse wave velocity; **B**, carotid artery distensibility; **C**, endothelial function; **D**, intima-media thickness of the carotid artery. Data are mean for each age group.

tension-associated changes in large artery structure has been debated. Liao *et al.* [16] evaluated the prospective relation between baseline arterial elasticity and the development of hypertension in a population sample. After 6 years of follow-up, one standard deviation decrease in arterial elasticity was associated with a 15% greater risk of hypertension, independent of established risk factors for hypertension and the level of baseline blood pressure. These results suggest that lower arterial elasticity is causally related to the development of systolic hypertension.

Chronologic and biologic aging in arterial hemodynamics

The age-related changes in cardiac function, circulatory hemodynamics, lipid metabolism, and detoxification of reactive oxygen species all contribute to morbidity and mortality in the elderly. Although age is an outstanding risk factor for high blood pressure, stroke, and coronary artery disease, the precise pathophysiologic mechanisms underlying these observations are presently unknown.

Telomeres, the end of chromosomes, prevent DNA "erosion" and are subject to attrition with each division of somatic cells. Recent experimental data support the concept

that telomere length might serve as a biologic clock, not only at the cellular level but probably also at the systemic level [17•,18]. Of interest is the fact that homocysteine, a known risk factor for atherosclerosis [19], enhances the rate of telomere attrition per replicative cycle in cultured human vascular endothelial cells [20]. To a large extent, this effect appears to be mediated by reactive oxygen species. Recently, it was shown that both pulse pressure and pulse wave velocity are inversely correlated with telomere length independent of chronologic age [17••]. These observations suggest that pulse pressure and pulse wave velocity might be markers of the biologic age of the vascular system.

Established cardiovascular risk factors and arterial stiffness

Obesity is associated with decreased aortic elasticity. The rise in blood pressure following gain in body weight is associated with profound changes in cardiovascular-renal physiology, including increased plasma volume, enhanced tubular sodium reabsorption, an initial decrease in total peripheral resistance, increased heart rate, activation of the sympathetic nervous system, and activation of the systemic renin-angiotensin-aldosterone axis [21]. Adipose tissue

secretes the hormone leptin, which increases sympathetic activity [21].

Adults with familial hypercholesterolemia have a significantly lower aortic distensibility than control subjects [22]. The changes in vessel wall properties due to hypercholesterolemia may be due to 1) impaired responses to endothelial relaxing factors (such as nitric oxide), 2) an increased content of collagen and calcium subsequent to deposition of cholesterol in the vessel wall, and 3) a toxic effect of oxidized lipoproteins on the endothelium [23••].

Even in the young, cigarette smoking increases arterial stiffness, aortic blood pressure, and plasma von Willebrand factor (a marker of endothelial damage) [24,25]. More than 3800 chemicals present in tobacco smoke cause oxidative stress either directly or via biotransformation of these compounds. Smoking acutely increases sympathetic tone [26]. Furthermore, smoking decreases nitric oxide production, the primary vasodilator produced by endothelial cells [24].

Diabetes is associated with increased arterial stiffness and decreased endothelial function [27]. Glycation of proteins due to alterations in cellular metabolism remains a reasonable pathophysiologic link between hyperglycemia and the development of complications in diabetes. These chemically modified proteins may interact with cells in the vascular wall, inducing expression of cytokines and growth factors, which cause cross-linking of collagen molecules to each other [28], leading to enhanced loss of collagen elasticity with a subsequent reduction in arterial distensibility.

Homocysteine, a sulfur-containing amino acid that is formed in the metabolism of methionine to cysteine, behaves as an independent risk factor for cardiovascular disease. The two most important determinants of the plasma homocysteine concentration are folate status and renal function. From *in vitro* and animal models there is evidence that high homocysteine concentrations are associated with endothelial toxicity attributed to oxidative stress that results from auto-oxidation of homocysteine [29]. During this process hydrogen peroxide and superoxide are formed, which may increase low-density lipoprotein oxidation, and decrease the bioavailability of nitric oxide [29]. The decrease in nitric oxide leads to vasoconstriction. In hypertensive patients, plasma homocysteine is positively correlated with aortic stiffness as assessed by carotid-femoral pulse wave velocity, independent of sex, age, blood pressure, and renal function [30]. However, homocysteine-lowering therapy had no beneficial effect on carotid distensibility in patients with end-stage renal disease [31], or in healthy siblings of patients with premature atherosclerosis [32].

Diagnosis

According to the 2003 ESH/ESC guidelines for the management of arterial hypertension (World Health Organization [WHO]/International Society of Hypertension [ISH]) [8], the diagnosis of hypertension should be based on multiple

conventional blood pressure measurements taken on separate occasions. However, ESH/ESC recommends that consideration should be given to blood pressure self-recorded and/or ambulatory blood pressure monitoring before making therapeutic decisions [8]. A daytime ambulatory or self-recorded blood pressure of 135/85 mm Hg may be regarded as hypertensive [8].

Ambulatory and self-recorded blood pressure monitoring significantly increase the prognostic accuracy of conventional blood pressure readings, both in hypertensive patients [33] and in the general population [34]. The greater number of measurements, the absence of digit preference and observer bias, and the minimization of the white coat effect contribute to the greater reproducibility and consequently to the predictive superiority of ambulatory and self-recorded blood pressures over conventional pressures. In addition, a blunted fall in nocturnal blood pressure is a harbinger of an unfavorable outcome [35].

In the clinical setting, the main use of ambulatory blood pressure monitoring is to identify patients with white coat hypertension in whom antihypertensive drug treatment may be avoided. White coat hypertension is usually defined as an elevation of the clinic blood pressure in the presence of a normal daytime ambulatory blood pressure [36]. In older patients with isolated systolic hypertension, clinic and daytime ambulatory blood pressure measurements may differ largely. Event-based studies [37] have clearly demonstrated that the risk of cardiovascular disease is lower in patients with white coat hypertension than in those with higher ambulatory blood pressure even after controlling for concomitant risk factors. When daytime ambulatory blood pressure was below 130 mm Hg systolic and 80 mm Hg diastolic, the incidence of cardiovascular disorders did not differ between normotensive subjects and those with white coat hypertension [36]. In the Syst-Eur trial, patients with isolated systolic hypertension (conventional SBP 160 mm Hg or more) were classified according to daytime SBP into one of three subgroups: nonsustained hypertension (less than 140 mm Hg), mild sustained hypertension (140 to 159 mm Hg), and moderate sustained hypertension (160 mm Hg or more). Patients with nonsustained hypertension had smaller electrocardiogram (ECG) voltages and a lower incidence of stroke and of cardiovascular complications than patients with moderate sustained hypertension [38]. The counterpart of white coat hypertension is masked hypertension, a disorder characterized by a normal conventional blood pressure confirmed on repeated clinic visits, but an elevated daytime ambulatory blood pressure. Preliminary observations suggest that this condition is associated with more target-organ damage than observed in subjects with sustained normotension [39].

Conventional blood pressure measurement remains the standard for evaluating blood pressure. In patients with raised clinic blood pressure and either target-organ damage or a high cardiovascular risk profile, treatment can be started

without confirmation of the elevated clinic readings by automated measurement techniques. When, however, a raised blood pressure is the only detectable abnormality or when patients with a normal clinic blood pressure show unexplained target-organ damage, self-measurement, ambulatory monitoring, or both must be used to exclude white coat hypertension or masked hypertension, respectively. In the absence of other cardiovascular risk factors and signs of target organ damage, therapy of patients with white coat hypertension may be limited to lifestyle measures and annual follow-up of the ambulatory blood pressure [40].

Complications

Increased blood pressure may result in cardiac, cerebral, retinal, or renal complications. Within the scope of this article, only cardiovascular complications will be discussed.

The heart responds to hypertension with compensatory growth of the myocardium, thus resulting in left ventricular hypertrophy and, if left untreated, followed by dilatation and heart failure. Besides affecting the myocardium directly, hypertension causes marked adaptive changes in the circulation and is a major risk factor for coronary heart disease and stroke. In middle-aged Europeans and Americans, the main complication of hypertension is coronary heart disease, whereas in Asians and older people it is stroke [41]. Blacks tend to have higher levels of blood pressure and hypertension-related mortality rates than do nonblacks [42].

In a collaborative project [43] using data from nine prospective studies including 418,343 individuals between 25 and 84 years of age, mainly men (96%), an increase of 5 mm Hg diastolic, accompanied by a 9 mm Hg higher systolic pressure, conferred a 35% to 40% higher risk of stroke and a 20% to 25% higher risk of coronary disease. The Framingham Heart Study showed that after a 30-year follow-up, hypertensives compared with normotensives had a sixfold higher risk for heart failure and a twofold higher risk for intermittent claudication [44].

Randomized clinical trials provide data on the reversibility of the risk associated with hypertension, although usually follow-up is no longer than 3 to 5 years. In eight trials, 15,693 patients with isolated systolic hypertension were followed-up for 3.8 years (median). After correction for regression dilution bias, sex, age, and DBP, the relative hazard rates associated with a 10 mm Hg higher initial SBP were 1.26 ($P < 0.001$) for total mortality, 1.22 ($P = 0.02$) for stroke, but only 1.07 ($P = 0.37$) for coronary events. Independent of SBP, DBP was inversely correlated with total mortality, highlighting the role of pulse pressure as risk factor.

Outcome Trials

Placebo-controlled trials

The ultimate goal of treating patients with isolated systolic hypertension is not to reduce blood pressure, but to prevent the cardiovascular and renal complications of an

elevated SBP so that survival is prolonged and the quality of life is improved. Since 1991, three outcome trials have been published that addressed the question of whether in the elderly the cardiovascular risk conferred by isolated systolic hypertension is reversible by antihypertensive drug treatment. In all trials and subgroups combined [3•], among 7757 control patients, 734 deaths and 835 major cardiovascular complications occurred; in 7936 patients allocated active treatment, these numbers were 656 and 647, respectively. Median follow-up was 3.8 years. Overall, active treatment reduced total mortality by 13%, cardiovascular mortality by 18%, all cardiovascular complications by 26%, stroke by 30%, and coronary events by 23% [3•].

In the Systolic Hypertension in Europe (Syst-Eur) trial patients (60 years or older) with isolated systolic hypertension were randomized to active treatment ($n = 2398$), *ie*, nitrendipine, with the possible addition of enalapril and hydrochlorothiazide, or to matching placebos ($n = 2297$) [45]. The between-group difference in blood pressure amounted to 10.1/4.5 mm Hg ($P < 0.001$). Active treatment reduced the incidence of fatal and nonfatal stroke by 42% and that of major cardiovascular complications by 30%. Cardiovascular mortality tended to be lower on active treatment (-26% , $P = 0.08$), but all-cause mortality was not significantly influenced (-13% , $P = 0.28$) [45,46]. Furthermore, active treatment reduced the incidence of mild renal dysfunction (serum creatinine 176.8 $\mu\text{mol/L}$ or more) by 64% (13 vs five cases, $P = 0.04$) [47]. The relative benefits of active treatment were evenly distributed across the two sexes and across patients with and without a history of cardiovascular complications [48]. Further analysis also suggested similar benefit in patients who remained on nitrendipine monotherapy [49].

At randomization into the Syst-Eur trial, 492 patients (10.5%) had diabetes mellitus. In these patients, with adjustments for possible confounders, active treatment reduced all-cause mortality by 55%, cardiovascular mortality by 76%, all cardiovascular endpoints by 69%, fatal and nonfatal strokes by 73%, and all cardiac endpoints by 63%. The reductions in total mortality ($P = 0.04$), cardiovascular mortality ($P = 0.02$), and all cardiovascular endpoints ($P = 0.01$) were significantly larger in diabetic than in nondiabetic patients (Fig. 2) [50]. Furthermore, active treatment reduced the risk of proteinuria more ($P = 0.04$) in diabetic than in nondiabetic patients (71% vs 20%).

The Syst-Eur Vascular Dementia Substudy [51] investigated whether antihypertensive treatment could reduce the incidence of dementia. In total, 2418 patients were enrolled. After a median follow-up of 2 years in the double-blind trial, active treatment reduced the incidence of dementia by 50% ($P = 0.05$) from 7.7 to 3.8 cases per 1000 patient-years (11 vs 21 patients). Active treatment prevented mainly Alzheimer's dementia (eight vs 15 cases). These results were confirmed in the open-label follow-up study [52]. During extended follow-up, the number of incident cases of dementia increased from 32 to 64. Long-term active treatment ($n = 1485$) compared with control ($n =$

Figure 2. Adjusted relative hazard rates associated with active treatment as compared with placebo in diabetic and nondiabetic patients participating in the Syst-Eur trial. The relative hazard rates were adjusted for sex, age, previous cardiovascular complications, systolic blood pressure at enrollment, smoking status, and residence in eastern or western Europe. The *P* values are for the interaction between treatment and diabetes and indicate whether the treatment effect was significantly associated with the presence or absence of diabetes at enrollment. Cardiovascular events, stroke, and cardiac events included fatal and nonfatal events. The bars indicate the 95 % confidence intervals. The numbers above the bars indicate the benefit of the active treatment compared with placebo. (Adapted from Tuomilehto et al. [50].)

1417) reduced the incidence of dementia by 55%, from 7.4 to 3.3 cases per 1000 patient-years (43 vs 21 patients) [52]. Several reports suggest that calcium channel blockers, which cross the blood-brain barrier and bind to brain receptors located in areas affected by Alzheimer's disease, may confer specific neuroprotection [53]. However, the concept that antihypertensive therapy with long-acting dihydropyridines might protect against dementia needs further testing in controlled clinical trials.

The double-blind Syst-Eur trial ($P = 0.009$) [48] showed an interaction between treatment allocation and age. Randomization to active treatment was associated with a decreased relative risk of death in subjects aged 60 to 69 years (59%) and 70 to 79 years (58%), but with a slightly increased risk of death in patients aged 80 years or more (11%). Similarly, a meta-analysis of the results of controlled trials in hypertensive patients over the age of 80 years showed a nonsignificant 6% excess of death from all causes [54]. In view of the remaining uncertainty, the Hypertension in the Very Elderly Trial (HYVET) is currently investigating the potential benefit of antihypertensive drug treatment on stroke and other cardiovascular endpoints in the very elderly [55]. This trial will include a subgroup of patients with isolated systolic hypertension.

All available outcome trials in isolated systolic hypertension recruited patients with an SBP of 160 mm Hg or more. Currently no data are available showing that antihypertensive drug treatment reduces the risk of cardiovascular events in patients with borderline isolated systolic hypertension (SBP between 140 and 159 mm Hg and DBP less than 90 mm Hg) who have no previous cardiovascular complications and who are not exposed to other risk factors. Because the prevalence of this condition may be estimated to be around 20% [56] and because borderline isolated systolic hypertension is probably associated with an increased cardiovascular

risk [57], outcome trials in patients with borderline isolated systolic hypertension are urgently needed.

Comparative trials

Sixteen recent outcome trials compared old classes of anti-hypertensive drugs, such as diuretics and β -blockers, with new agents such as calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin type 1 receptor blockers, or α -blockers [58••]. These trials considered mainly patients with combined systolic and diastolic hypertension. Some trials [59–62] included subgroups of patients with isolated systolic hypertension. However, none of the trials provided specific estimates of the treatment differences in patients with isolated systolic hypertension. In all 135,842 patients with systolic and diastolic hypertension combined, old and new drugs provided similar protection against total and cardiovascular mortality and fatal and nonfatal myocardial infarction. Calcium channel blockers, including (+8%, $P = 0.07$) or excluding (+10%, $P = 0.02$) verapamil, as well as angiotensin type 1 receptor blockers (+24%, $P = 0.0002$) resulted in better stroke prevention than did the old drugs, whereas the opposite trend was observed for ACE inhibitors (–10%, $P = 0.03$). The risk of heart failure was higher ($P < 0.0001$) on calcium channel blockers (+33%) and β -blockers (+102%) than on conventional therapy involving diuretics [58••]. These results should be interpreted with caution. Indeed, more detailed analyses demonstrated that most differences in specific cardiovascular endpoints were due to design features, gradients in achieved SBP, or both factors [58••].

Conclusions

Since age and blood pressure are continuous variables with no discernible transition points where there is a sudden

increase in morbidity and mortality, arbitrary definitions must be used for classification. Unlike DBP, SBP increases progressively with age. The characteristic changes of SBP and DBP with age lead to an increase in pulse pressure, which has emerged as a new and potentially independent risk factor reflecting the biologic aging of the vascular system.

Arterial stiffness is increasingly recognized as an important factor underlying cardiovascular complications in the elderly. Population and clinical studies suggest that SBP should be the primary target of antihypertensive therapy, although consideration of SBP and DBP together improves risk prediction.

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