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Perspectives on Systolic Hypertension

The Framingham Study

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SUMMARY Diastolic hypertension has been widely and justifiably accepted as a cause of cardiovascular mortality. However, it has also been accepted that the cardiovascular sequelae of hypertension derive chiefly from the diastolic component. Because systolic and diastolic pressure are usually highly correlated it is not easy to dissociate the effects of each. Statistical analysis suggests that systolic pressure is actually the more potent contributor to cardiovascular sequelae. Even isolated systolic pressure elevation is associated with an excess cardiovascular mortality. At low diastolic pressures (i.e., < 95 mm Hg), risk rises with the level of systolic pressure. Also, isolated systolic hypertension is most ominous in the elderly, in whom it is highly prevalent.

Isolated systolic hypertension was related to the occurrence of "direct" complications as well as to atherosclerotic sequelae. It was also associated with excess mortality, taking into account rigid vessels as judged from pulse-wave recordings. Trials to determine whether the treatment of isolated systolic hypertension is efficacious for avoiding its demonstrated excess cardiovascular morbidity and mortality are urgently needed.

ELEVATED BLOOD PRESSURE is recognized as a powerful precursor of the major cardiovascular diseases, including coronary heart disease, cerebrovascular disease, cardiac failure and occlusive peripheral arterial disease.¹⁻³ Although blood pressure is an acknowledged risk factor for cardiovascular disease, it is taught clinically and the conviction of most physicians is that the diastolic component is the chief determinant of the cardiovascular sequelae of hypertension.⁴⁻⁶ The level of diastolic pressure rather than the level of systolic pressure is the current indication for treatment of hypertension.⁷ There is, however, abundant evidence that both the systolic and diastolic components of the blood pressure predict the occurrence of cardiovascular disease.¹⁻⁸ Epidemiologic evidence indicates that systolic pressure may be a better predictor than diastolic pressure for most cardiovascular sequelae of hypertension.⁹

The importance of isolated systolic hypertension as a precursor of cardiovascular disease remains controversial despite increasing evidence relating it to cardiovascular morbidity and mortality.¹⁰ In this report we present data on isolated systolic hypertension in the Framingham cohort. Data are presented on the prevalence of isolated systolic hypertension and on the relation of isolated systolic hypertension to the incidence of cardiovascular disease.

Methods

The data presented are from the Framingham Study, which was initiated in 1948 with a cohort of 5209 men and women ages 30-62 years who have been examined biennially since that time. This report examines data on systolic and diastolic blood pressure obtained during 20 years of follow-up.

At each biennial examination three pressures were obtained, one by a nurse and two by the examining physician. The first blood pressure was taken by a nurse soon after the clinical phase of the examination began. A physician took readings at the beginning and end of the physical examination near the end of the clinic visit. Readings were taken in the left arm of the seated subject using a mercury sphygmomanometer with cuffs large enough to fit the most obese arm. The first reading taken by the physician is used in this report.

Criteria for the various cardiovascular end points, the sampling procedure, response rates and laboratory methods have been published elsewhere.¹¹ All new cardiovascular events were reviewed by a panel of investigators and only those meeting minimal criteria were accepted. Follow-up on mortality has been reasonably complete with only 3% completely lost in the 20 years. About 85% have appeared for each biennial examination at the clinic; interim information was available on hospitalization and physician visits.

Logistic analyses were done to assess the effect of blood pressure on the incidence of cardiovascular disease. The estimates of the logistic coefficients were obtained using an iterative maximum likelihood approach as suggested by Walker and Duncan.¹² For all analyses where multiple measurements were available (e.g., blood pressure), the information from these multiple determinations was pooled. This pooling was accomplished by considering each examination for each participant as an independent observation. Thus, a person could contribute follow-up to more than one age group and more than one blood pressure classification.

For the present analyses, isolated systolic hypertension was defined as systolic pressure 160 mm Hg or above with diastolic pressure below 95 mm Hg.

Results

Diastolic hypertension has been widely and justifiably accepted as a cause of cardiovascular, renal and cerebrovascular mortality.^{4-6, 13} Framingham data

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TABLE 1. Average Standardized Logistic Coefficients for Regression of Specified Cardiovascular Events on Systolic and on Diastolic Blood Pressure: Framingham Study 20-year Follow-up, Men and Women 45-74 Years Old

Event	No. of events		Men		Women	
	Men	Women	SBP	DBP	SBP	DBP
CHD	445	287	0.3299	0.2697	0.4630	0.3519
CHD death	98	47	0.4081	0.3424	0.5380	0.4091
CVA	107	118	0.5966	0.5324	0.6096	0.5924
CHF	117	102	0.5298	0.3264	0.5466	0.3563
Death	501	355	0.2770	0.1850	0.2662	0.1709
CV death	283	168	0.3672	0.2452	0.4859	0.2996

Abbreviations: CHD = coronary heart disease; SBP = systolic blood pressure; DBP = diastolic blood pressure; CVA = cerebrovascular accident; CV = cardiovascular; CHF = congestive heart failure.

confirm this clinical impression. Because systolic and diastolic pressures are highly correlated, it is difficult to categorically dissociate the effects of these two components of the blood pressure. One may, however, compare the impact of each on particular cardiovascular end points. Standardized bivariate (age and pressure) logistic coefficients for the regression of cardiovascular events on systolic and diastolic pressures were computed. Because they are expressed in standardized units, the magnitude of these coefficients may be compared directly to assess the relative impact of systolic and diastolic pressure without concern about the different range of values for each component of the pressure (table 1). This reveals that systolic pressure is the more potent contributor to all clinical sequelae of hypertension.

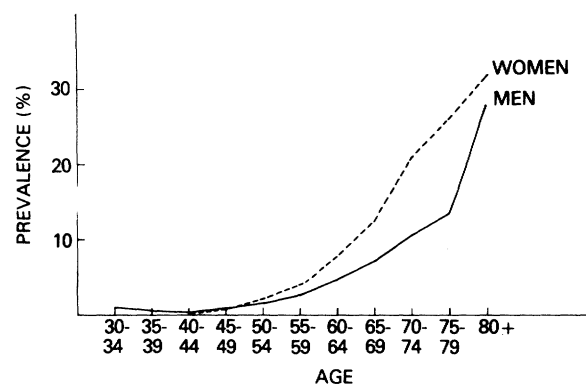
Blood pressure is a continuous variable and the risk of cardiovascular sequelae rises with the level of pressure with no discernible transition points defining an abrupt escalation of risk. However, arbitrary cut points are widely used to define "hypertensives." Hence, an exploration of the risk of cardiovascular sequelae associated with these arbitrary blood pressure categories and their prevalence is worthwhile.

Prevalence of Isolated Systolic Hypertension

The prevalence of isolated systolic hypertension increases with age in both sexes but is relatively uncommon until age 45 years (fig. 1). The prevalence is low in both sexes at younger ages. Beyond age 55 years the prevalence increases in both sexes, with the rise among females being steeper than among males.

Hazards of Isolated Systolic Hypertension

Isolated systolic hypertension is associated with a substantial (two- to fivefold) excess risk of death from



NUMBER:											
MEN	591	1628	2539	3282	3975	3617	2817	1795	985	350	22
WOMEN	694	1979	3178	4107	4971	4741	3692	2463	1413	573	32

FIGURE 1. Prevalence of isolated systolic hypertension by age and sex. The Framingham Study, 24-year follow-up.

all causes and from cardiovascular disease in particular (table 2). Also, among persons with diastolic pressures below 95 mm Hg, risk rose in relation to systolic pressure at all ages under consideration and just as steeply in the elderly as in the middle aged.

It has been stated that isolated systolic hypertension is often "burned-out" diastolic hypertension and that the excess risk due to isolated systolic hypertension may derive from the previous diastolic elevation.¹⁰ While we cannot exactly specify those with "burned-out" diastolic hypertension, if at each biennial examination we exclude from the population at risk anyone who previously had a diastolic pressure higher than 95 mm Hg, there is still a pronounced excess risk of cardiovascular disease associated with isolated systolic hypertension (table 3).

It has been suggested that systolic hypertension is

TABLE 2. Systolic Hypertension and Death from All Causes and from Cardiovascular Disease: Framingham Study 20-year Follow-up, Men and Women 55-74 Years Old

	Men		Women	
	Rate/1000	Ratio*	Rate/1000	Ratio*
Death (all causes)	56.0	2.0	29.3	2.0
Cardiovascular disease death	29.5	1.8	24.4	4.7

*Rate in patients with isolated systolic hypertension to rate in normotensives.

TABLE 3. Two-year Incidence of Cardiovascular Disease Among Persons 55-74 Years with Isolated Systolic Hypertension*

	Cardiovascular disease rate (Rate/1000)	Factor of increased risk (O/E)†
Men	113.0	3.5
Women	50.3	3.8

*Excludes persons previously diagnosed as having diastolic blood pressure ≥ 95 mm Hg at any time during the 20-year follow-up.

†O/E is the ratio of rate among those with isolated systolic hypertension to rate among normotensives.

only a sign of arteriosclerosis, which is responsible for the cardiovascular sequelae.¹⁰ At the eighth annual examination, pulse-wave recordings were obtained on the Framingham cohort.¹⁴ The depth of the dicrotic notch was graded from 1 to 4 (4 = absence of notch). While more sophisticated assessments of the rigidity of the arterial system exist, some evidence suggests that the depth of the dicrotic notch is related to arterial rigidity i.e., the prevalence of coronary heart disease in men.¹⁴ Subjects without a dicrotic notch have a higher mean pulse pressure and a higher prevalence of isolated systolic pressure than those with a dicrotic notch (table 4). The results of a multivariate logistic analysis using the depth of the dicrotic notch, systolic pressure and age as independent variables and excluding those with elevated diastolic pressures from the population at risk are presented in table 5. The level of systolic pressure is still significantly related to the incidence of cardiovascular disease.

It has also been claimed that lability of pressure has not been taken into account in epidemiologic studies of isolated systolic hypertension.¹⁰ It is difficult to see how this could influence the results. All blood pressure is labile and high pressures, both systolic and diastolic, are actually more labile than low ones.¹⁵ Three blood pressure determinations were obtained for each person at each examination. If we quantify lability by the standard deviation of these three pressures, then multivariate analysis, taking into account the lability of the systolic pressure as well as its level and the age of the subject, reveals no evidence that lability of pressure independently influences cardiovascular risk (table 6).

TABLE 5. Standardized Multivariate Regression Coefficients for Cardiovascular Disease Within 6 Years of Pulse-wave Reading, Excluding from Risk Anyone with Diastolic Pressure ≥ 95 mm Hg

	Men 45-74 years		Women 45-74 years	
	Coefficient	t	Coefficient	t
Systolic blood pressure	0.4300	3.74	0.3708	2.90
Pulse wave	0.2246	1.65	-0.0204	-0.14

TABLE 6. Cardiovascular Disease vs Systolic Level, Lability and Age. Framingham Study 20-year Follow-up, Ages 45-74 Years

	Standardized multiple logistic coefficients	
	Men	Women
SBP lability	0.027	0.080
SBP level	0.357*	0.420*
Age	0.303*	0.458*

* $p < 0.001$.

Abbreviation: SBP = systolic blood pressure.

Discussion

Hypertension with systolic pressure exceeding 160 mm Hg and diastolic pressures below 95 mm Hg is a common, hazardous and probably treatable condition. Isolated systolic hypertension is a common problem in people over age 55 years, especially in women (fig. 1). Although this condition may be considered an accompaniment of aging due to progressive loss of arterial elasticity, it cannot be considered innocuous. People with isolated systolic hypertension, even in advanced age, have a substantially increased risk.

Hemodynamic studies of isolated systolic hypertension have indicated that in those over age 35 years there is generally a normal heart rate, a decreased left ventricular ejection rate and a reduced cardiac index.¹⁶ There is also an increased peripheral resistance, a disproportionate rise in systolic pressure relative to diastolic pressure and a widening pulse pressure. These changes could reflect atherosclerotic loss of arterial compliance.

In persons under age 35 years with isolated systolic hypertension, the hemodynamics may differ. In this

TABLE 4. Age-adjusted Mean Pulse Pressure and Age-adjusted Prevalence of Isolated Systolic Hypertension by Level of Pulse-wave Recording in Men and Women 45-74 Years Old

Pulse-wave category*	Number		Age-adjusted mean pulse pressure (mm Hg)		Age-adjusted prevalence of isolated systolic hypertension (%)	
	Men	Women	Men	Women	Men	Women
	1	228	46	51.2	54.9	1.2
2	222	148	53.2	54.4	6.0	0.4
3	314	643	58.3	59.0	13.7	13.4
4	34	143	59.6	62.0	14.3	21.7

*Depth of dicrotic notch: 4 = absent; 1 = pronounced.

age group there is generally a hyperdynamic circulation as indicated by an increased cardiac output and heart rate and a normal peripheral resistance.^{10, 16} Over time this may evolve into the pattern of normal cardiac output with high peripheral resistance characteristic of essential hypertension. Data from the Framingham Study derived from subjects over age 30 years can shed no light on the evolution of isolated hypertension or on the hazards associated with it below age 35 years.

Diastolic hypertension is a documented precursor of cardiovascular, renal and cerebrovascular mortality and a direct cause of left ventricular failure, intracerebral hemorrhage, dissecting aneurysm, nephrosclerosis, encephalopathy and the necrotizing arteriolitis of malignant hypertension.¹⁰ Reduction of diastolic pressure results in a reduction of these direct complications.^{7, 17} However, the same can be said for systolic pressure elevation with which diastolic elevations are almost invariably associated, and for correction of systolic pressure elevations, which almost always accompany lowering of diastolic pressure. If the Veterans Administration study data were analyzed according to systolic rather than diastolic pressure, the same results would undoubtedly be shown regarding the danger of uncontrolled pressure and the efficacy of lowering elevated pressure.⁷ However, the benefit of correcting isolated systolic hypertension is in genuine doubt.

Isolated systolic hypertension may not be a homogeneous entity, but neither is diastolic hypertension.¹⁰ Isolated systolic hypertension is most commonly attributed to inelastic large arteries, presumably due to arteriosclerosis, but not necessarily atherosclerosis. Other causes of isolated systolic hypertension include aortic insufficiency, atrioventricular dissociation, Paget's disease, coarctation of the aorta, severe anemia and hyperthyroidism.¹⁰ All of these disorders can cause cardiac failure and other sequelae of hypertension. These etiologies account for a small proportion of isolated systolic hypertensives.

It has been claimed that isolated systolic hypertension is only an innocent accompaniment of inelastic rigid arteries as a result of aging. This is attributed to arteriosclerosis and as a consequence, isolated systolic hypertension should accompany predominantly atherosclerotic cardiovascular sequelae. However, in the Framingham cohort isolated systolic hypertension was also found to be related to hypertensive cardiac failure and to stroke, as well as to coronary heart disease and occlusive peripheral arterial disease. The pulse-wave data also indicate that systolic hypertension per se is associated with the cardiovascular sequelae whether the vessel is rigid or not. Further, isolated systolic hypertension 10 or more years before any clinical event appears is also related to cardiovascular sequelae.

Experience in geriatric hospitals suggests that isolated systolic hypertension can be treated effec-

tively with properly selected antihypertensive agents in the majority of those so afflicted. If patients are selected carefully and prudently, leisurely implementation of therapy is used; this can often be accomplished without inducing intolerable postural hypotension and other severe side effects. However, whether such treatment will prevent cardiovascular sequelae or prolong life remains to be shown for persons with isolated systolic hypertension. In view of the demonstrated hazard of this condition, a controlled trial to determine the efficacy of treatment is needed. In the elderly, who have a high prevalence of systolic hypertension, it is more important to control the hypertension in order to improve the quality than prolong the length of life. In the elderly a disabling stroke or strangling chronic cardiac failure is not a pleasant reward for reaching a venerable stage in life.

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