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Editor's Comments

NEWS FROM FRAMINGHAM: THE AASK STUDY AND INSULIN RESISTANCE—IS IT DUE TO NO NO?

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This issue of ***Current Concepts in Hypertension*** continues the description of ongoing clinical trials and outcome studies by bringing new information from the oldest of the observational studies in cardiovascular disease now in its 51st year (the Framingham Study). Dr. Stanley Franklin summarizes the most recent findings from Framingham regarding the age-related changes in systolic and diastolic pressure and provides insight into the importance of pulse pressure, an important predictor of cardiovascular events associated with aging.

Dr. Kenneth Jamerson provides descriptive information regarding one of the most recent intervention trials designed to examine the causes and possible approaches to prevention of end-stage renal disease in African-American hypertensives (the AASK study). The background and rationale for the trial are discussed, along with the experimental design. The results of this important study should be available in the next 3 years.

Dr. Helmut Steinberg provides additional information regarding the possible role of nitric oxide production in the pathophysiology of insulin resistance, a commonly encountered abnormality in hypertensive subjects. These observations may help explain the association between insulin resistance and blood pressure.

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THE EFFECT OF AGE AND HYPERTENSION ON SYSTOLIC, DIASTOLIC, MEAN, AND PULSE PRESSURE: THE FRAMINGHAM HEART STUDY

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Previous studies have shown a progressive increase in blood pressure (BP) with aging in industrialized societies, beginning in childhood and progressing throughout adulthood. We attempted to characterize these age-related changes in BP in both normotensive and untreated hypertensive subjects in a population-based cohort from the original Framingham Heart Study and to infer underlying hemodynamic mechanisms.[1]

There was a linear rise in systolic blood pressure (SBP) from age 30 through 84 years and a concurrent increase in diastolic blood pressure (DBP) and mean arterial pressure (MAP) until about 50 years of age (Fig. 1, red line). After age 50 to 60 years, DBP declined, pulse pressure (PP) rose steeply, and MAP leveled off while SBP continued to show a linear increase throughout the geriatric years.

The almost parallel rise in SBP, DBP, and MAP up to age 50 can best be explained by an increase in peripheral vascular resistance (PVR).[2] The reduction in DBP has been attributed to "burned out" diastolic hypertension but this decrease in DBP was noted in both normotensive and untreated hypertensive subjects. Furthermore, of those hypertensives whose SBPs were >140 mm Hg, only a third had antecedent DBP of >90 mm Hg prior to the onset of declining DBP values. Two thirds of the hypertensive population had maximum DBP of <90 mm Hg throughout their entire course. Similarly, the concept of "selective survivorship" has been postulated as a cause of the late decline in DBP. However, this was not consistent with persistence of the late fall in DBP after removal of all deaths and patients with nonfatal myocardial infarction (MI) or congestive heart failure (CHF) from the study sample (Fig. 1, blue line). A further hypothesis, namely an age-related decrease in cardiac output as the cause for the late fall in DBP, is inconsistent with the late rise in SBP. Similarly, increase in PP is not due to bradycardia for there was a step-wise increase in heart rate with rising SBP (Table 1). The most plausible explanation for the BP pattern from age 50 onward, therefore, is an increase in large artery stiffness caused by intrinsic structural abnormalities.[2,3] With age-related stiffening of the aorta, there is decreased elasticity and greater peripheral runoff of stroke volume during systole. With less blood remaining in the aorta at the beginning of diastole and with diminished elastic recoil, DBP decreases and the diastolic decay curve becomes steeper.[3]

In this study, the standard cuff pressures showed a leveling off of MAP values in both normotensive and hypertensive groups after age 50 to 60. In the hypertensive groups MAP actually decreased after the seventh or eighth decade (Fig. 1). MAP, derived from the standard equation and using brachial artery readings, is thought to approximate PVR in young subjects when cardiac output is not elevated. The fall in DBP secondary to the increase in large artery stiffness explains why the MAP equation grossly underestimates PVR after 50 years of age.

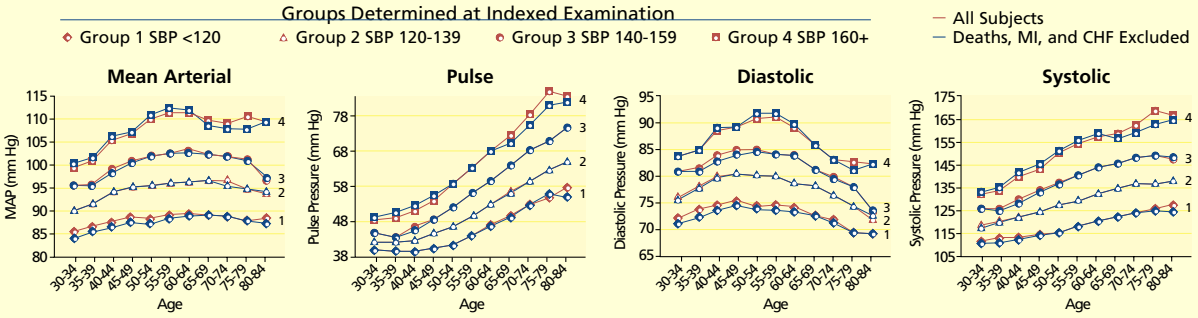
Table 1 The Effect of Systolic Blood Pressure on Heart Rate: The Framingham Heart Study

SBP Group	Mean BP (mm Hg)	Heart Rate[a] (beats/min)	Standard Error	Group Differences (*P* value)
1	111/70	72.7	±0.64	0.0001
2	129/77	75.0	±0.44	0.0001
3	148/83	77.5	±0.57	0.0001
4	173/90	80.5	±0.78	0.0001

Heart rates were determined at baseline examination in normotensive and untreated hypertensive subjects by systolic blood pressure groupings. Group 1 had <120 mm Hg; group 2, 120 to 139 mm Hg; group 3, 140 to 159 mm Hg; group 4, >160 mm Hg. The study cohort consisted of 2036 subjects (890 men and 1146 women). BP = blood pressure, SBP = systolic blood pressure.
[a] All heart rates were age and sex adjusted.
Data derived from Franklin SS, et al. Circulation 1997;96:308-315.

The Framingham findings also support the concept of an interaction between aging and hypertension in the progressive fall of DBP and rise of SBP. Subjects with mean baseline BPs of 111/70 (Fig. 2, group 1) had no rise in PP and only a minimal increase in MAP from age 30 to 49 years. Nevertheless, this group of normotensive subjects showed a significant rise in PP and fall in DBP after age 60 years, presumably caused by an increase in large artery stiffness secondary to aging. In contrast, subjects with baseline mean BPs of 173/90 (Fig. 2, group 4)

Figure 1 Arterial Pressure Components by Age



Arterial pressure components by age (group averaged data for all subjects and with deaths, MI, and CHF excluded) with averaged blood pressure levels from all available data from each subject within 5-year age intervals by SBP groupings 1 through 4. The red line represents the entire study cohort (2036 subjects) and the blue line the study cohort with deaths, nonfatal MI, and CHF excluded (1353 subjects).
Reproduced with permission of Lippincott Williams & Wilkins, from Franklin SS, et al. Circulation 1997;96:308-315.

THE RATIONALE FOR THE AFRICAN-AMERICAN STUDY OF KIDNEY DISEASE AND HYPERTENSION

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The pathophysiology of hypertensive nephrosclerosis and its ultimate sequela, hypertensive end-stage renal disease (HTN ESRD), constitutes a greater disease burden for African Americans. A current estimate, based on epidemiologic studies, is that 7 million African Americans have essential hypertension.[1] The United States Renal Data System 1993 Annual Report[2] indicated an incidence of 12,000 African-American ESRD patients in 1990, of which 4880 had hypertension as the primary cause of kidney failure. This represents a population attributable risk of 40% compared to 23% in whites. Between 1983 and 1990, the incidence of HTN ESRD increased by 500% in African Americans. Total enrollment in the ESRD program is expected to reach 250,000 by the year 2000.[3]

The African-American Study of Kidney Disease and Hypertension (AASK) is a clinical trial sponsored by the National Institutes of Health. It is designed to compare the effects of two levels of BP control (MAP 102 to 107 and <92 mm Hg) and 3 different antihypertensive drug regimens (angiotensin-converting enzyme inhibitor [ACEI], calcium channel blocker [CCB], or β-blocker) on renal function in African Americans. The study is being conducted at 21 centers in the United States. Approximately 1100 men and women, aged 18 to 70 years with a diagnosis of hypertension and renal impairment (iothalamate clearance 20 to 65 mL/min) were recruited. The basis of the evaluation for two levels of BP control arises, in part, from observations in the Modification of Diet in Renal Disease (MDRD) study. African Americans in this study randomized to the low BP target (<92 MAP) had a decline in glomerular filtration rate (GFR) that was about half the rate observed in participants randomized to the usual BP group (MAP 102 to 108 mm Hg). This result inferred that targeting a DBP of 75 mm Hg was more protective of renal function than the more traditional target DBP of 90 mm Hg. However, because there were so few African Americans in the MDRD study, it could not be determined whether lower BP was truly beneficial. Subjects are followed

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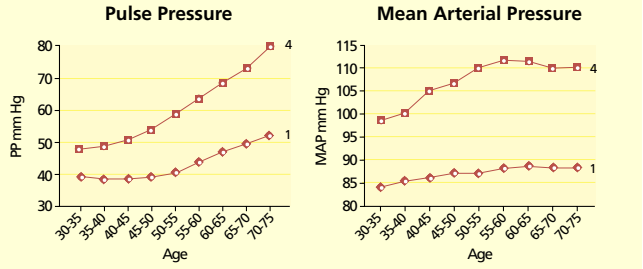
THE EFFECT OF AGE AND HYPERTENSION ON SYSTOLIC, DIASTOLIC, MEAN, AND PULSE PRESSURE: THE FRAMINGHAM HEART STUDY

Figure 2 The Effect of Age and Hypertension on Pulse Pressure and Mean Arterial Pressure



Arterial pressure components by age. Averaged pulse pressure levels and mean arterial pressure levels from all available data are from each subject within 5-year age intervals by systolic blood pressure (SBP) groupings. Group 1 had a mean baseline BP of 111/70; Group 4 had a mean baseline BP of 173/90.
Adapted from Franklin SS. Circulation 1997;96:308-315.

showed a steeper rise in PP and a steeper fall in DBP after age 60 than was observed in group 1 subjects. This divergent rather than parallel tracking pattern observed in all 4 SBP groups has been referred to as the horse-racing effect, there being a close correlation between the speed of the horse and its position in the race. These findings suggest a linkage between hypertension left untreated and subsequent acceleration of large artery stiffness. Although increased PVR may initiate essential hypertension, acceleration of large artery stiffness is the driving force leading to the steeper rise of SBP after age 50 in the hypertensive groups 3 and 4 as compared to normotensive groups 1 and 2 (Fig. 1).

Age-related BP changes were generally similar in both sexes but, as noted previously, our findings showed young women had lower BPs than similarly aged men (Fig. 3). These differences gradually narrowed and eventually reversed beyond age 60 years. Sex differences in BP were more marked in hypertensive subjects. These findings suggest there may be sex differences in arterial stiffening, with young women having more compliant vessels. With the onset of menopause this difference may be lost, with a resulting acceleration in arterial stiffening.

The clinical implications that can be derived from this study are that, after the sixth decade of life: (1) increasing PP and decreasing DBP are surrogate measurements for large artery stiffness; (2) large artery stiffness rather than vascular resistance becomes the dominant hemodynamic factor in both normotensive and hypertensive subjects; and (3) hypertension, left untreated, may accelerate the rate of development of large artery stiffness. This, in turn, can perpetuate a vicious cycle of accelerated hypertension and further increases in large artery stiffness.

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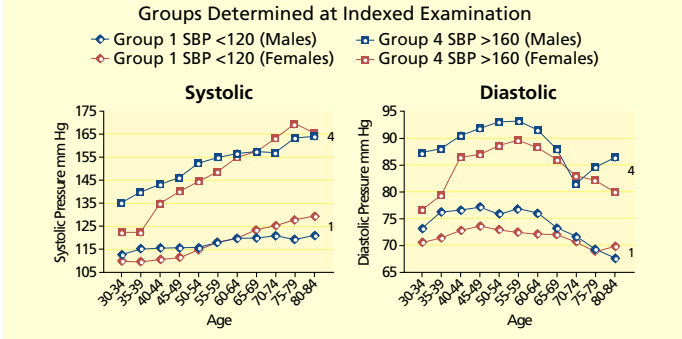
Figure 3 Arterial Pressure Components Averaged by Age and Sex



Averaged blood pressure levels from all available data for each subject with 5-year age intervals by SBP groupings 1 versus 4.
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for 4 years. The study endpoints are a 50% decline in GFR or time to renal failure, defined as dialysis.

There is substantial evidence that the treatment of hypertension may not adequately affect the progression to renal failure. Subjects with hypertension and impaired renal function may not improve and even progress despite normalization of BP.[4-6] While clinical trials and epidemiology surveys define hypertension by the application of discrete categorical specifications (DBP ≥90 mm Hg), the deleterious effect of elevated BP on the kidneys and other target organs is a continuous risk function. There are inherent problems in this arbitrary categorization of a continuously distributed attribute or characteristic. One such problem of immediate relevance is what level of BP in an individual (member of a population) is to be considered optimal with respect to the prevention of renal parenchyma disease progression and, simultaneously, safe with respect to adequate perfusion of other vital vascular beds?

An analysis of the Multiple Risk Factor Intervention Trial (MRFIT) cohort[1] indicates that DBP <95 mm Hg is associated with a positive reciprocal creatinine slope (+0.0012 dL/mg/yr) compared to patients with DBP ≥95 mm Hg which was associated with a negative reciprocal creatinine slope (-0.0013 dL/mg/yr) after 6 years of followup. This beneficial effect of lower DBP was observed in whites but not in African-American participants in the MRFIT cohort. At 10.5 years of followup, there was no significant reduction in renal mortality in either African Americans or whites, nor was there any relationship between baseline level of creatinine and mortality.[7]

The concept of a renoprotective antihypertensive regimen (e.g., the selective ability of specific antihypertensive agents to reverse, restitute or prevent the pathophysiologic progression of hypertensive renal disease when compared to an equally effective alternative antihypertensive regimen) offers a potentially useful therapeutic strategy to ameliorate hypertensive renal disease. This consideration is particularly relevant to African Americans in whom effective control of systemic hypertension may not translate into protection from renal parenchyma disease.

A substantial body of evidence indicates two main classes of pharmacologic agents (ACEIs and some CCBs) may have renoprotective effectiveness under experimental conditions.[8,9] ACEIs have been demonstrated to decrease postglomerular capillary resistance and normalize glomerular capillary pressure, thus protecting the kidney from the development of arteriolar nephrosclerosis.[10,11] An additional nonrenin-mediated renoprotective effect of ACEIs may be the enhancement of bradykinin and cellular vasodilatory prostaglandin biosynthesis.[12] Experimental evidence also indicates CCBs may protect the glomerular microcirculation from hypertensive injury by way of afferent arteriolar dilation and reduction of glomerular capillary pressure.[13,14] These experimental evidences of the renoprotective effects of ACEIs and CCBs have been supported by several clinical trials that have demonstrated a reversal, stabilization, or slowing of the progression of renal function in diverse hypertensive patient populations with varying degrees of renal insufficiency.[13,15-20] Unfortunately, most of these clinical studies suffer from one or more methodologic deficiencies relating to inadequate sample size, inappropriate patient selection criteria, relatively short follow-up period, defective control group or lack of control, and the utilization of suboptimal measures of renal function.[21] An important limitation of the available clinical studies is inclusion of few or no African Americans, the subgroup with the highest incidence of hypertensive renal parenchymal disease. Bauer et al.[22] reported a clinical trial of 23 patients with one of the longest follow-up periods. After 3 years of followup, patients with essential hypertension and moderately impaired renal function (inulin clearance <80 cc/min) treated with enalapril showed a 33% higher inulin clearance compared to placebo. Sunderrajan et al.[23] demonstrated a mean 62% improvement in GFR at 16 months in a group of 18 patients with pretreatment GFR ≥80 cc/min/1.73m^2.

Table 2 Baseline Characteristics of AASK Participants (n=1094)

Baseline Characteristics	
Age	54.5 years
Blood pressure	150/95 mm Hg
Gender (M/F)	60%/40%
Weight	90 kg
GFR	46 mL/min/1.73 m^2
Years of hypertension	14 years
Antihypertensive drugs at entry (N)	2.4
Smokers	31%
With private health insurance	40%
With education <grade 12	40%
Employed	36%
Income at poverty level	50%

The AASK study began with a 2-year pilot phase to examine the feasibility of a long-term clinical trial. The first 98 subjects underwent renal biopsy. This demonstrated that the pathologic feature of hypertensive nephropathy was not unique in African Americans.

With the initiation of the full scale trial, 21 clinical centers enrolled 1100 subjects. The baseline characteristics of the group can be found in Table 2. There is currently greater than 93% compliance with all clinic visits, 75% pill taking compliance, and dramatic changes in BP (average BP during followup is 137/84 mm Hg). The study is progressing in a manner such that there will be adequate power to answer all study question. We anxiously anticipate the results in 2002.

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HYPERTENSION AND INSULIN RESISTANCE: IS DEFECTIVE NITRIC OXIDE PRODUCTION ONE MISSING LINK?

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Both essential hypertension and insulin resistance increase the risk of cardiovascular disease. The prevalence of each condition is ~30% and still rising. Insulin resistance is defined as decreased rates of glucose uptake in response to insulin. Insulin resistance is associated with a number of metabolic abnormalities such as dyslipidemia and hypertension. For the last decade it has been acknowledged that both conditions occur together more commonly than predicted by chance, suggesting a mechanistic relationship between the conditions. Whether insulin resistance causes hypertension and/or whether hypertension induces insulin resistance is unknown. Both scenarios are possible and not mutually exclusive. In this short review, evidence will be presented that impaired endothelial function with decreased nitric oxide (NO) production may be one link between insulin resistance and hypertension.

NO is generated from L-arginine in a reaction catalyzed by the enzyme NO synthase which is expressed constitutively in the vascular endothelial cells. NO generation is modulated by shear stress and a variety of hormones such as insulin, estrogen, atrial natriuretic factor, epinephrine, bradykinin, and acetylcholine. NO diffuses through the subendothelial space to the vascular smooth muscle cell where it activates the enzyme guanylate cyclase which increases levels of cyclic GMP, ultimately resulting in vasorelaxation and increased local flow. At the local level, this NO action will augment the supply of substrate (i.e. insulin and glucose) that may result in increased tissue metabolism. At the level of the whole body, this NO action will lead to lower BP levels. Thus, it is conceivable that impaired endothelial NO production may contribute to BP elevation and insulin resistance.

Hypertension has been shown to display impaired blood flow increments in response to the endothelium-dependent vasodilator acetylcholine.[1] In contrast, the blood flow response to the NO donor sodium nitroprusside, which is endothelium independent, was normal suggesting that the observed defect was due to decreased release of NO at the level of the vascular endothelium and not to reduced NO action at the level of the vascular smooth muscle. This notion was recently supported by Forte and colleagues[2] who, using sophisticated tracer techniques, demonstrated decreased total body NO production rates in subjects with essential hypertension. Thus, hypertension is associated with impaired endothelial function and decreased NO production.

In 1990, Laakso and coworkers[3] demonstrated that insulin increased leg blood flow in a dosage dependent fashion. Furthermore, leg blood flow increments and rates of glucose metabolism correlated positively and strongly, suggesting that insulin's metabolic and vascular effects are coupled. Importantly, insulin's stimulation of blood flow was blunted in insulin resistant obese and Type II diabetic subjects. In normal insulin-sensitive subjects, insulin-mediated vasodilation is accompanied by increased sympathetic nervous system activity and increased cardiac output with a small reduction in MAP, indicating marked vasodilation at the level of the skeletal muscle vasculature.[4]

Our group was able to show that this insulin mediated vasodilation depends on the release of NO.[5] Because insulin-mediated vasodilation is blunted in insulin resistant obese and Type II diabetic subjects we hypothesized that insulin resistance is associated with impaired endothelial function. In fact, the response to the endothelium-dependent vasodilator methacholine, but not to the endothelium-independent vasodilator sodium nitroprusside, was significantly reduced in the insulin resistant obese and diabetic subjects.[6] Moreover, Petrie and colleagues,[7] using the NO synthase inhibitor L-NMMA, showed that NO-dependent blood flow, a measure of endothelial NO production, correlated positively with insulin sensitivity. Taken together, these data indicate insulin resistance is associated with impaired endothelial function and decreased NO production rates.

Insulin mediated increments in skeletal muscle blood flow correlated positively with glucose uptake rates (insulin sensitivity) and inversely with resting BP.[8] Therefore, it is not surprising that insulin resistant hypertensive subjects exhibited decreased insulin mediated vasodilation.[9] However, not all forms of hypertension are associated with insulin resistance[10] and it is not known whether these patients exhibit impaired NO production. Importantly, BP elevation induced by either norepinephrine[11] or angiotensin II[12] did not cause insulin resistance. These data suggest that elevated BP, per se, may not be sufficient to cause insulin resistance—especially when the NO system is left intact. On the other hand, inhibition of NO production in the leg induced insulin resistance (decreased insulin-mediated glucose uptake)[13,14] and small increments in BP, and systemic inhibition of NO production in animals[15] produced both insulin resistance and hypertension. These data suggest that impaired endothelial function with decreased NO production may be necessary for the development insulin resistance accompanied by BP elevation.

In summary, impaired endothelial function and decreased NO production is one abnormality shared by insulin resistance and essential hypertension. Given the multiple antiatherosclerotic actions of NO, impaired NO production may not only explain the clustering of hypertension and insulin resistance but also the macrovascular disease observed with hypertension and with insulin resistance.

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